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Nutrition, Neurodevelopment And Mental Health

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Nutrition, Neurodevelopment And Mental Health

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Thesis submitted for the degree of Doctor of Philosophy in
Epidemiological Psychiatry and Psychosis

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Abstract

There is increasing awareness for the potential effects of nutrition on mental health. Specifically, researchers are interested in the benefits of omega-3 polyunsaturated fatty acids (n-3 PUFA) and vitamin D on brain development and psychological well-being.

The main objective of this thesis is to examine evidence for the relationship between nutritional intake, neurodevelopment, psychotic and depressive symptoms. This thesis consists of a series of studies designed to test several hypotheses. A review and meta-analysis tested the hypothesis that maternal fish oil intake/omega 3 supplementation during pregnancy is associated with better cognitive performance in offspring. Next, we used data from the Swedish Women's Lifestyle and Health Study, to test the hypothesis that low UV exposure is associated with more positive psychotic symptoms and with more severe depressive symptoms. For the purpose of this study we use UV exposure data as a primary index for vitamin D. Firstly, the results of meta-analysis showed that for the measure of overall cognitive ability the standardised difference in means (SMD) was estimated to 0.10 (95% CI, -0.01 to 0.20; $p=0.07$) and for memory functions the SMD was 0.21 (95% CI, 0.01 to 0.41; $p=0.04$). The observational studies showed better overall cognitive ability with pooled OR of 1.92 (95% CI, 1.61 to 2.30; $p<0.001$) and for the domain of language and verbal skills the OR was 1.93 (95% CI, 1.37 to 2.73; $p<0.001$) among children of mothers consuming 2 to 3 fish servings per week during pregnancy. Maternal intake of fish oil during pregnancy is associated with improved cognitive abilities in the offspring. Secondly, the association between sun exposure and psychotic experiences was evaluated by quantile regression models. 34 279 women were included in the analysis. Women who reported no sunbathing holidays and two or more weeks of sunbathing holidays scored higher on the Community Assessment of Psychic Experience (CAPE) scale than women exposed to one week of sunbathing holidays across the entire distribution, when adjusting for age and education. Similarly, compared with women who reported a history of a single sunburn, the women with none or two or more sunburns showed higher scores on the CAPE scale with more women in the right part of the distribution. Thirdly, women who reported a history of two or more sunburns showed positive association with depressive symptoms, compared to history of a single sunburn, when adjusting for age and education. The findings suggest that in a population based cohort of middle aged women, both low and high sun exposure is associated with increased level of positive psychotic experiences and high sun exposure is associated with an occurrence of depressive symptoms.

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Dedication

This is dedicated to my family who supported me on this journey. Thank you for your love and unremitting encouragement!

To my fiancé- I have never met anyone who believes in me more. Thank you for making me more than I am.

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“Knowing is not enough, we must apply.

Willing is not enough; we must do.”

-Goethe

Chapter 1 Introduction

1.1 About schizophrenia and psychosis

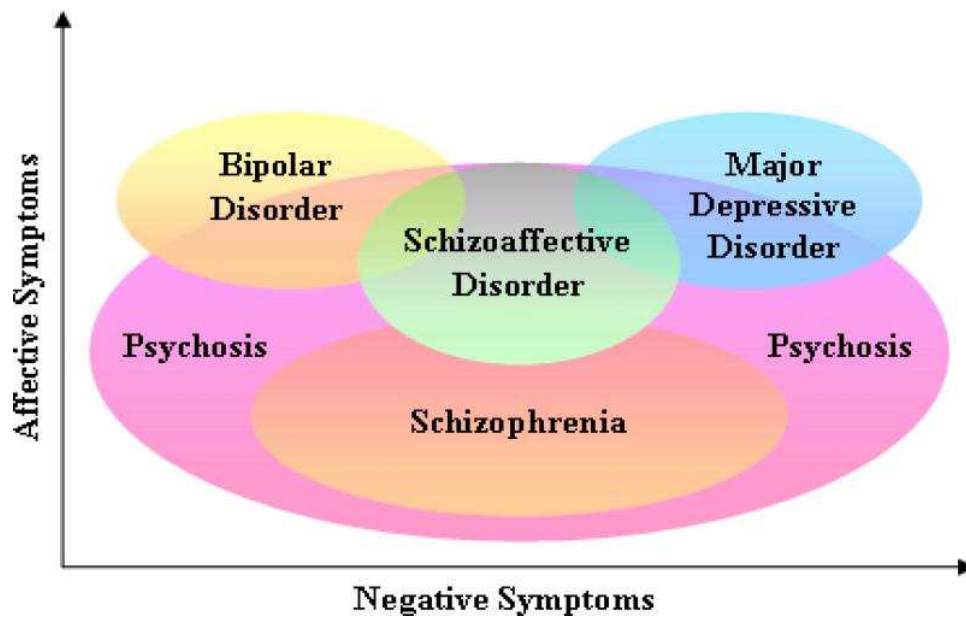
Approximately one in a hundred people will experience schizophrenia and might experience a collection of symptoms referred to as either positive or negative symptoms (Jablensky, 2000). According to the DSM-5 and ICD-10 (American Psychiatric Association, 2013; World Health Organization, 1992), the primary positive symptoms of psychosis are: hallucinations (auditory, visual, olfactory, and tactile), delusions (persecution, nihilism, grandiosity, control, thought possession, disorganised speech (stream of thought, flight of ideas, loosening of associations); disorders of behaviour (gross excitement/overactivity); motor abnormalities (catatonia, gross psychomotor retardation). Schizophrenia spectrum and other psychotic disorders include schizophrenia, other psychotic disorders, and schizotypal (personality) disorder. They are defined by abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behaviour (including catatonia), and negative symptoms (American Psychiatric Association, 2013).

Delusions are false beliefs that are firmly held on inadequate grounds; are not affected by rational argument or evidence to the contrary; furthermore it is not a conventional belief that the person might be expected to hold given her educational, cultural and religious background. Several types of delusions are recognised, either by the characteristics or the theme of the delusion. Hallucinations are perceptions experienced in the absence of an external stimulus to the corresponding sense organ. It differs from an illusion in being experienced as originating in the outside world (or sometimes within the person's body) but not within the mind (e.g. mental imagery). A hallucination can be in the mind, with an illusion there is a stimulus which is misinterpreted. Disorganised speech is normally inferred by examining abnormalities in speech. Disorders of behaviour or motor abnormalities comprise a marked increase in the normal levels of activity, characterised by hyperactivity, or a marked decrease in activity, characterised by catatonia, or very slowed or fixed movements.

Different disorders share common phenomenological features. This overlap in symptomology is perhaps most prominent in regards to symptoms of psychosis. For example, psychotic features such as positive (hallucinations, delusions), negative (apathy, avolition, and asociality), and disorganized (disorganized speech or behaviour) symptoms are the cornerstones of schizophrenia, however, they are also observed across a broad spectrum of diagnoses outside

of the “psychotic disorders” category as defined by the current edition of the DSM. Consequently, an individual presenting with auditory hallucinations and delusional beliefs might be diagnosed with schizophrenia, schizoaffective disorder, bipolar disorder or major depressive disorder (DeRosse, Malhotra, & Lencz, 2012) (see figure 1).

Figure 1 Symptoms of psychosis across multiple diagnostic categories.



1.1.1 Cognitive impairments and psychotic illnesses

In chapter 3, I introduce the concept of cognitive functions related to omega 3 deficiency which are important to study due to cognitive impairments being documented as core features of schizophrenia and are related to functional status and other aspects of illness (Green, 1996, Heinrichs and Zakzanis, 1998). Further, lower cognitive ability in childhood is associated with increased risk of future schizophrenia (Aylward, Walker, & Bettes, 1984; Jones, Rodgers, Murray, & Marmot, 1994). Although they are common in schizophrenia, they are not specific to this illness. They are evident also in the subjects with affective disorders (Gilvarry *et al.*, 2001, Goldberg *et al.*, 1993, Gruzelier *et al.*, 1988, McGrath *et al.*, 1997, Sweeney *et al.*, 2000, Zubieta *et al.*, 2001) and other forms of functional psychosis (Mitrushina *et al.*, 1996, Zanelli *et al.*, 2010). However, it appears that neuropsychological impairments are more severe in schizophrenia. In several studies, patients with schizophrenia have been shown to be more impaired in a range of cognitive tests than patients with bipolar disorder and other functional psychotic conditions (Gilvarry *et al.*, 2001, Goldberg, 1999, Mitrushina *et al.*, 1996, Seidman *et al.*, 2002).

Neuropsychological abnormalities are evident many years before the overt expression of any psychotic symptoms (Aylward *et al.*, 1984, David *et al.*, 1997, Davidson *et al.*, 1999, Hoff *et al.*, 1999, Jones *et al.*, 1994, Reichenberg *et al.*, 2002). Dating back to the work of Spearman (Spearman, 1928), a distinction has been made between general and specific cognitive abilities. Two widely used indices of generalised neurocognitive performance have been applied in research: general measures of intelligence quotient (IQ), and composite scores or profiles derived from test batteries comprising multiple neuropsychological tests. Although both provide a measure of an individual's overall cognitive functioning, the results of these assessments often do not overlap to a substantial degree. Neuropsychological test batteries typically focus on assessment of multiple cognitive abilities, such as memory, executive functions, and attention, and these include a strong component of novelty of testing requirements. IQ tests, on the other hand, have a lesser emphasis on specific abilities and novelty and greater emphasis on the assessment of crystallized abilities (Bratti and Bilder, 2006).

1.1.2 Aetiology and treatment of schizophrenia

As is the case with many mental disorders, the cause of schizophrenia is not known although both genetic and environmental factors have been implicated (Jim van Os & Kapur, 2009). There are a number of theories relating to neurotransmitter imbalances and functional magnetic resonance imaging (fMRI) studies have shown a broad array of brain abnormalities. The

conventional treatment for schizophrenia is usually long-term treatment with antipsychotic medication. A nutritional approach works alongside conventional treatment and there is preliminary evidence that omega-3 is an effective adjunct to antipsychotics (Emsley, Oosthuizen, & van Rensburg, 2003).

The field of psychosis has long been aware that schizophrenia is more common in those born in winter and spring when sun exposure is minimum or none existing (Davies, Welham, Chant, Torrey, & McGrath, 2003). The prevalence of schizophrenia is associated with latitude – a finding first described by Fuller Torrey over 25 years ago (Torrey, 1977) and since replicated in systematic reviews (Davies et al., 2003). These findings have led to the hypothesis that low vitamin D (especially during early life) may be implicated in aetiology of schizophrenia (J. J. McGrath, Eyles, et al., 2010; J. J. McGrath, Burne, Féron, Mackay-Sim, & Eyles, 2010). The impact of vitamin D or sun exposure on brain changes in adult life has not been investigated.

1.1.3 Psychotic experiences in the general population

Recently it has been suggested that psychosis exists in the general population as a continuous phenotype rather than as an all-or-none occurrence (J van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Population-based studies have confirmed that psychotic experiences, for example, delusions and hallucinations, are indeed prevalent in the community (Johns et al., 2004; Kelleher & Cannon, 2011; Therman, Suvisaari, & Hultman, 2014). Early epidemiological studies included psychotic experiences in their research and focused on exploring potential risk indicators for later conversion to full psychosis (Kelleher & Cannon, 2011). This type of research has an interesting rationale as many of the risk factors associated with psychotic experiences in non-clinical population are also associated with schizophrenia and psychosis (J. J. McGrath et al., 2015). Further results from similar studies revealed that psychotic experiences are also related to the subsequent onset of a wide range of common mental disorders, including anxiety, depression, and substance use disorders (Saha et al., 2011; Varghese et al., 2011). Consequently, awareness is growing that the presence of psychotic symptoms may reflect a vulnerability to a wide range of adverse mental health outcomes (in addition to psychotic disorders).

1.2 Major Depressive Disorder

According to the NICE guidelines, depression is defined as a broad and heterogeneous diagnostic grouping, central to which is depressed mood or loss of pleasure in most activities (NICE, 2009). Major depressive illness is common in the general population and it affects up to one sixth of the population, perhaps more (Doris, Ebmeier, & Shajahan, 1999). Reported by the WHO in 2015, globally, an estimated 350 million people of all ages suffer from depression. Depression is the primary cause of disability worldwide, and is a major contributor to the overall global burden of disease. Depression is more common in women than men (Bierut et al., 1999; Weissman & Olfson, 1995).

DSM-5 criteria for depression list the key 2 symptoms:

- Depressed mood most of the day, almost every day, indicated by your own subjective report or by the report of others. This mood might be characterized by sadness, emptiness, or hopelessness.
- Markedly diminished interest or pleasure in all or almost all activities most of the day nearly every day and/or marked loss of interests or pleasure

(at least one of the above symptoms must occur most days, most of the time for at least 2 weeks).

As reported by Ingram, 2012, symptoms of depression may vary according to an individual's age and culture. Children who are depressed, for instance, may express symptoms of irritability rather than sadness or they may fail to make expected weight gains rather than lose weight. In contrast, older adults are more likely than younger adults to experience symptoms such as loss of appetite, loss of interest, and thoughts of death. Cultural differences also exist in the report of depressive symptoms (Ingram, 2012). For example, studies of American, Korean, Philippine, and Taiwanese college students found that Taiwanese students reported the lowest numbers of somatic symptoms and the highest numbers of affective symptoms (Kalibatseva, Leong, Kalibatseva, & Leong, 2011). Hence, one's age and culture seems to affect not whether depression is experienced, but rather how it is expressed (Ingram, 2012).

Although the cause of depression is still unclear, it is becoming clear that a number of diverse factors are likely to be associated, both genetic and environmental (NICE, 2009). Several socio-demographic correlates are found consistently across countries and cross-national data also document associations with numerous adverse outcomes, including difficulties in role transitions

(e.g., low education, high teen child-bearing, marital disruption, unstable employment), reduced role functioning (e.g., low marital quality, low work performance, low earnings), elevated risk of onset, persistence, and severity of a wide range of secondary disorders, and increased risk of early mortality due to physical disorders and suicide (Yirmiya, 2000).

1.2.1 Depressive symptoms and its variations in the general population

Data on prevalence of several symptoms of depression were consistently reported in general population samples. One study found that, of the nine symptoms assessed, the most frequently occurring were dysphoric mood (17.8%), increased sleep (15%), and loss of interest in other people or activities previously enjoyed (11.8%). The author of the paper concluded that the findings provided evidence that various symptoms of depression may be more common in the general population than previously suspected (Henderson & Pollard, 1992). Depressive symptoms have a high prevalence worldwide and have been associated with common physical and mental health problems (Bland, 1997; Phillips et al., 2009). Additionally, depressive symptoms have been considered as leading cause of mortality and morbidity, meaning they have become the most important public health concern (Ferrari et al., 2013).

The seasonal variation of depressive symptoms has also received a considerable amount of attention in recent years. A specific form of seasonality, seasonal affective disorder (SAD) (Rosenthal, 1984) is known as winter depression. Magnusson concluded that in the general population, depressive symptoms peak in winter, and the most extreme form of this disposition, SAD, appears to be a relatively common in the general population (Magnusson, 2000). This overview of epidemiological studies on SAD reported the prevalence estimates of SAD across 20 retrospective studies varied from 0% to 9.7%. SAD was more prevalent at higher northern latitudes, but the prevalence varied across ethnic groups (Magnusson, 2000).

1.3 A link between nutrition and mental health

The biological mechanisms underlying the aetiology of schizophrenia and psychotic symptoms and depression are mainly unknown. Genetic constitution is important, but environmental factors like an unhealthy lifestyle with a poor diet may be involved. Therefore it is important to understand an overall link between mental health and nutrition. Chapter 4 and 5 of the thesis include the examination of the link between psychotic and depressive symptoms in the general population to

vitamin D from the UV exposure. I also evaluated in my meta-analysis (chapter 3) the potential association between omega 3 deficiency in pregnant women and their children's cognitive functions.

The relationship between schizophrenia and nutrition is diverse and complex. Potential nutrient deficiencies are some of the most prominent concerns (Georgieff, 2007). Research indicates that individuals with schizophrenia tend to have diets that are higher in energy and fat, and lower in fruits and vegetables, vitamin D and omega 3 (Georgieff, 2007).

Not much is understood about the connection between nutrition and depression while it is easily understood how a connection between nutritional deficiencies and physical illness could develop. For example, depression is typically thought of as strictly biochemical-based or emotionally-rooted (Kohatsu, 2005). However, nutrition can play a key role in the onset as well as severity and duration of mental illness such as schizophrenia or depression (Payne, 2010). Many of the evident unhealthy food patterns that precede depression are the same as those that occur during depression. For instance, an increased risk of depression has been associated with higher intake of trans fatty acids (Sánchez-Villegas et al., 2011), fast food and commercial bakery (Martínez-González & Sánchez-Villegas, 2015).

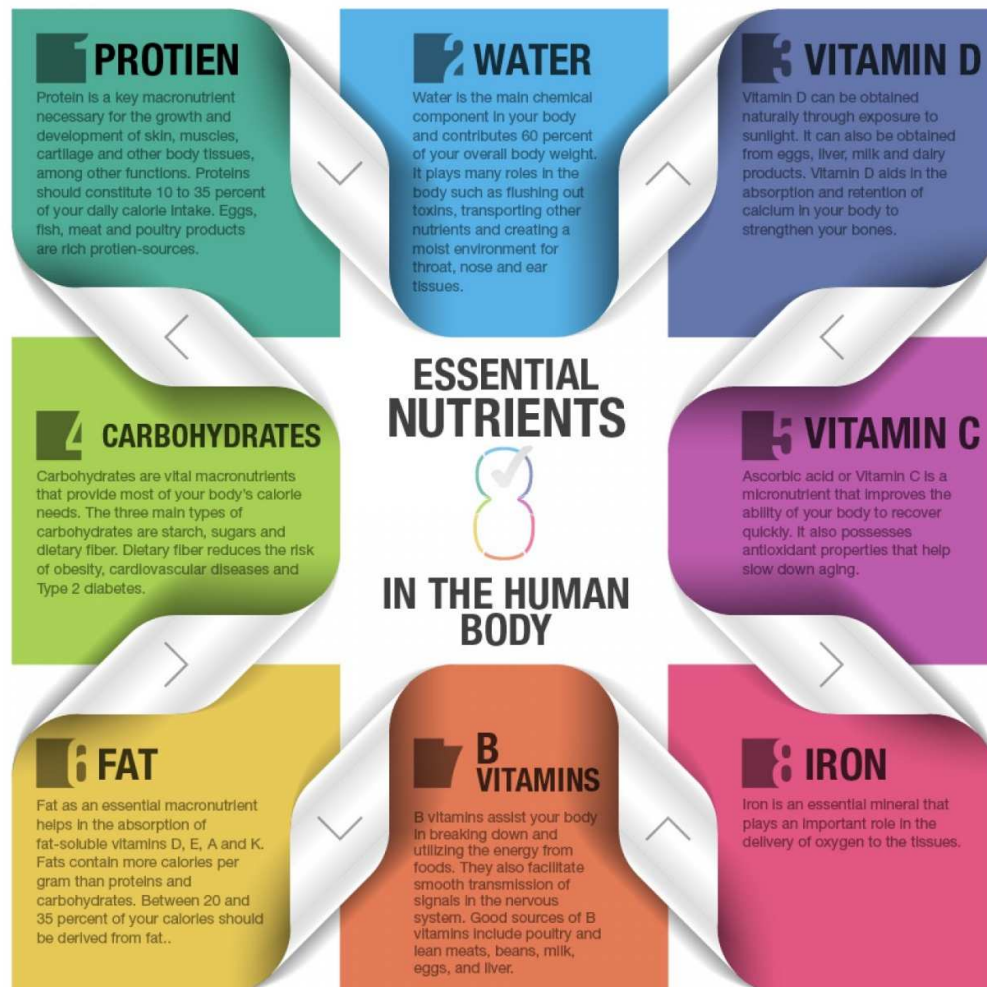
.Nutritional neuroscience is an emerging discipline shedding light on the fact that nutritional factors are intertwined with human cognition, behaviour, and emotions.

The dietary intake pattern of the general population in many European and American countries reflects that they are often deficient in many nutrients, especially essential vitamins (i.e. vitamin D), minerals, and omega-3 fatty acids (Rao, Asha, Ramesh, & Rao, 2008). Additionally, low maternal fish consumption during pregnancy is reported to increase the risk for a low IQ and suboptimal neuro-developmental outcomes in childhood (Hibbeln et al., 2007), factors that in turn are associated with an increased risk for adult mental disorders like schizophrenia. The Finish study of adult's prevalence of depressive symptoms and their relationship to fish consumptions showed that depressive symptoms in adults are common and the likelihood of having depressive symptoms was significantly higher among infrequent fish consumers than among frequent consumers (Tanskanen et al., 2001). Fatty fish is a rich dietary source of essential fatty acids and vitamin D, both of which could be implicated in the development of schizophrenia and depression throughout the lifespan. However, not much has been investigated on psychotic or depressive symptoms in non-clinical populations and their relation to nutrients status.

1.3.1 What are nutrients?

Nutrients are chemical compounds needed for growth, repair, energy, and regulation of body functions. According to the British Nutrition Foundation, macronutrients (carbohydrate, protein and fat) are essential nutrients that provide energy for the body and are required in large amounts in the diet. They provide our bodies with energy and the building blocks for growth and maintenance of a healthy body. Micronutrients (vitamins, minerals and water) are essential for the proper functioning of every system in the body and are required in smaller amounts than macronutrients (<http://www.nutrition.org.uk/>). Figure 1 presents the primary essential nutrients in the human body.

Figure 2 Essential Human Nutrients



Note 1 Adapted from the website <https://nutrilent.eu/understandingnutrients/>

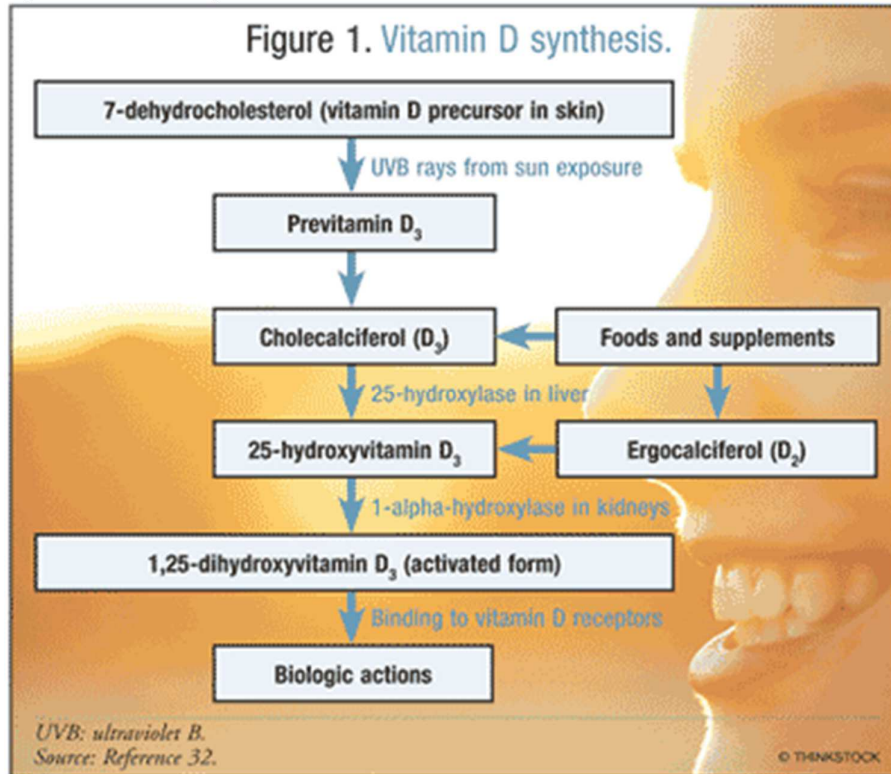
1.3.2 Nutrients and the brain

Nutrients play a critical role in cell proliferation, DNA synthesis, neurotransmitter and hormone metabolism, and are important components of enzyme systems (Zimmermann, 2011). Several studies suggest that nutrition has an important role for normal brain development prenatally, in childhood, as well as during adult life (Gómez-Pinilla, 2008). Nutrition is an important factor in brain development and deficiencies in several nutrients have been shown to have implications for brain and physical development. The most well-known example is probably folate acid. Folate acid and choline have a role in the closure of the foetal neural tube, and prenatal folate deficiency has been associated with neural tube defects (NTD) (Shaw, Carmichael, Yang, Selvin, & Schaffer, 2004). There is also evidence for association between folate intake before pregnancy and language development (Roth et al., 2012). These and other findings have led to worldwide fortification of foods with folate to prevent deficiency in pregnant women. Folate intake before pregnancy has recently been associated with lower risk for autism and language development (Roth et al., 2012).

1.3.3 Vitamin D - more than just strong bones

One of the nutrients discussed and examined in this thesis (chapter 3 and chapter 4) is vitamin D known as the sunshine vitamin. Although it's called a vitamin, it is a fat-soluble vitamin that acts as a steroid hormone (Yetley et al., 2009). Hormones are compounds produced in one part of the body and transported to another part of the body where they apply a specific regulatory or functional effect. In this case, vitamin D the body makes vitamin D from cholesterol through a process triggered by the action of the sun's ultraviolet B (UVB) rays on the skin (Calcium, Ross, Taylor, Yaktine, & Valle, 2011). Figure 1 presents the synthesis of vitamin D in humans. Sensible sun exposure can be an excellent source of vitamin D for both children and adults (Holick, 2004, 2005). Vitamin D was originally known for its role in reducing the risk of rickets, but in the past three decades the benefits of vitamin D were extended to protection against many non-calcemic diseases (Grant, 2009; Harvey et al., 2009). For example, decreased muscle function and increased fall risk in elderly people; prostate, breast and colorectal cancers; diabetes mellitus; and other health problems have been associated to low circulating levels of 25-hydroxyvitamin D (Grant, 2009; Muszkat, Camargo, Griz, & Lazaretti-Castro, 2010)

Figure 3 Vitamin D Synthesis.



Note 2 Adapted from Lau AH, How PP. The role of the pharmacist in the identification and management of secondary hyperparathyroidism. US Pharm. 2007;32(7):62–72.

There is increasing evidence for a link between vitamin D status and brain function (DeLuca et al., 2013). The first indirect evidence for vitamin D and its role in brain development and function was discovered and described by Stumpf et al (1982) who reported on vitamin D and its metabolites in the cerebrospinal fluid of healthy adults. The authors revealed that vitamin D receptors are widely spread in the embryonic brain prominently in the neuro-epithelium and proliferation zones (D. W. Eyles, Smith, Kinobe, Hewison, & McGrath, 2005; Stumpf, Sar, Clark, & DeLuca, 1982). The first real indications related to vitamin D and its role in brain function was provided by the presence of its receptor in the central nervous system (CNS). Later clues from animal studies (in

the neonatal and adult rats) added further weight to the hypothesis that vitamin D signalling is involved in brain function. These studies identified vitamin D receptors in several brain regions such as temporal, orbital and cingulate cortices, thalamus, accumbens, amygdala, olfactory system and pyramidal neurons of the hippocampus (Burkert, McGrath, & Eyles, 2003; Prüfer, Veenstra, Jirikowski, & Kumar, 1999; Veenstra et al., 1998). As for the human brain, later evidence for distribution of the vitamin D receptor was reported for the first time by Eyles et al providing clues the CNS' ability to synthesise (1,25(OH)₂D) the active form of vitamin D from 25 hydroxyvitamin D (25(OH)D), which is the precursor inactive form, a 'storage' form of vitamin D used to monitor serum levels (D. W. Eyles et al., 2005). This suggests that serum levels might influence the autocrine and paracrine production of 1,25(OH)₂D, the active form of vitamin D, in the CNS, challenging the assumption that the brain is solely dependent on circulating 25(OH)D crossing the blood–brain barrier (D. W. Eyles et al., 2005; Hosseinpour & Wikvall, 2000).

1.3.4 Omega 3 and brain functions

Lately, there has been increased interest in the role of essential fatty acids (EFA) in neurodevelopment. The two core fatty acids found in grey matter are omega-3 which is DHA (docosahexaenoic acid) and arachidonic acid (omega-6, AA) (Benton, 2010). DHA accumulation in the brain and in other organs depends on the amount and types of omega-3 fatty acids in the diet, and on dietary intake of omega-6 fatty acids which interact and compete with omega-3 fatty acids in the fatty acid metabolic pathway (Guesnet & Alessandri, 2011; Innis, 2007). DHA is especially important as it is considered a building block of tissue in the brain (and retina), and it is responsible for forming neural transmitters, such as phosphatidylserine, which is important for brain function (Guesnet & Alessandri, 2011; Morse, 2012).

EFA play a central role in brain tissue and modulate membrane fluidity and volume (de Souza, Fernandes, & do Carmo, 2011). These fatty acids regulate gene expression in the brain. Cognitive-nutritional research suggests that essential fatty acids are critical for brain development and function (Innis, 2007). EFA cannot be interconverted because human cells lack the converting enzyme omega-3 desaturase. They are not synthesized endogenously by humans and need to take place in the diet in order to provide the proper nutrients from fatty acids (Simopoulos, 2011). Most studies focus on the role of essential fatty acids, especially omega-3 polyunsaturated fatty acids (PUFA), perhaps due to omega 3 being a main component of brain cell membrane and critical for optimal brain development (Karr, Alexander, & Winningham, 2011). Cognitive

development is influenced by many factors and there is evidence that malnutrition can impair cognitive functions (A Nyaradi, Li, Hickling, Foster, & Oddy, 2013). However, there is not enough research to date investigating the association between dietary patterns and neurocognitive development (Anett Nyaradi, Li, Hickling, Foster, & Oddy, 2013).

Maternal fish consumption (which is a rich source of omega-3) during pregnancy has been positively associated with cognitive development in offspring. It is important to examine the relationship between nutritional intake and cognitive development of the offspring because omega-3 supplementation may be a low-risk and cost-effective approach to improve some aspects of neurocognition. During the third trimester of pregnancy, fetuses require around 40-60mg of omega 3 per kilogram body weight per day and the appropriate level of omega-3 is crucial in the last trimester due to rapid growth of the baby's brain. During that time large amounts of DHA accumulate in the brain therefore indicating a demand for the nutrients (Bernardi et al, 2012). Cohort studies have reported that consumption of fish during pregnancy, especially oily fish containing Omega 3, is positively associated with better cognitive performance of their offspring (i.e., improved performance on tests of language and visual motor skills (Mendez et al 2009; Oken et al 2008) and higher scores on memory task (Mendez et al 2009). Moreover, Gale et al (2008) reported that children whose mothers had eaten fish in late pregnancy had a higher verbal IQ compared to offspring of mothers that did not eat fish. Higher consumption of fish oil in pregnant women is also linked to offspring's better performance on digit span test which measures working memory (Boucher et al. 2011). There is some evidence suggesting that prenatal fatty fish consumption (four times a week) has positive effects on the offspring's cognitive abilities compared to mothers with no fish intake (at 18 months after birth) (Daniels, Longnecker, Rowland, & Golding, 2004). Helland et al. (2003) reported higher IQ at age 4 in children of mothers supplemented with cod liver oil (rich source of omega 3) from week 18 until 3 months after delivery than children of mothers supplemented with corn oil ($n = 36$; 106.4 [7.4] vs 102.3 [11.3]). Findings from observational studies provide a stronger support for more frequent fish intake during pregnancy and its association with improved offspring's cognitive function. The randomized controlled trials (RCTs), however, provide mixed results (Oken & Belfort, 2010). For example, in the intention-to-treat analysis, supplementing pregnant mothers with omega 3 did not benefit infant's cognitive performance (Gould, Smithers, & Makrides, 2013).

1.4 Nutrients and health

Nutrients are important not only for physical health, but also for optimal mental development and functioning. As reported by the World Health Organization (WHO), poor nutrition can lead to reduced immunity, increased susceptibility to disease, impaired physical and mental development, and reduced productivity (<http://www.who.int/uv/faq/uvhealtfac/en/>).

1.4.1 The known effects of UV on human health

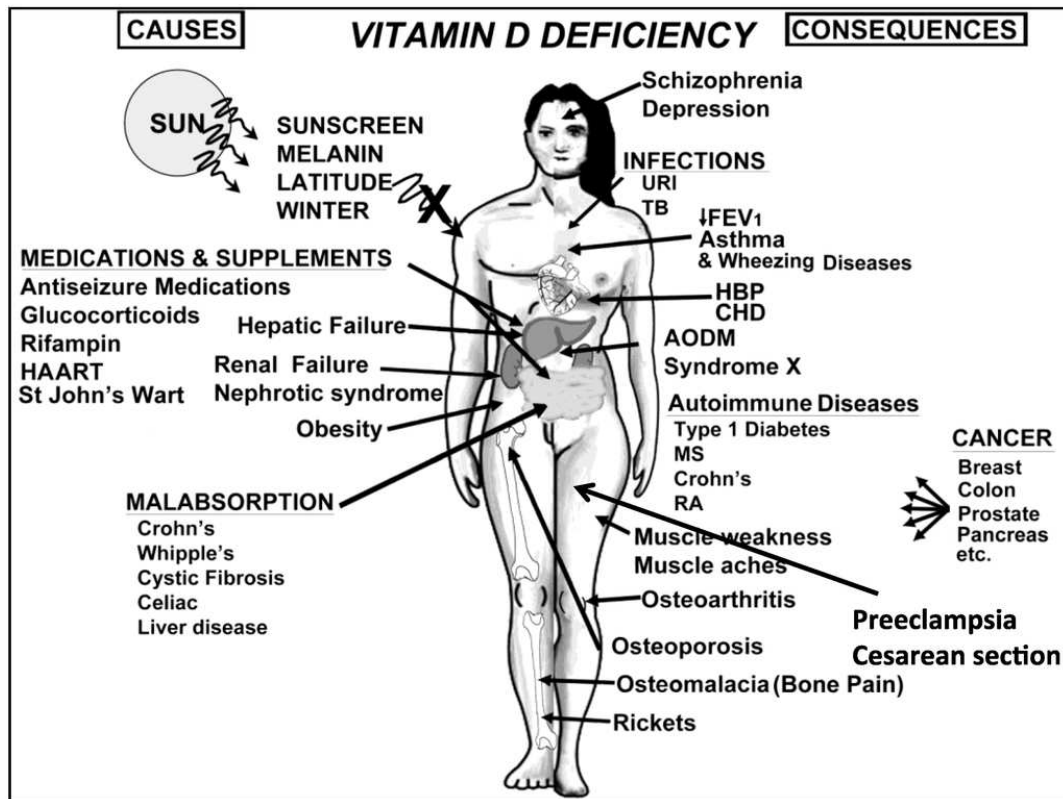
Sunlight and vitamin D are the main exposures of interest in this thesis in chapter 4 and 5. Exposure to sunlight is thought to increase the brain's release of a hormone called serotonin. This is associated with boosting mood and helping a person feel calm and focused (Young, 2007). In general, people have a feeling of wellbeing when exposed to sunlight. As early as in 1900s Finsen noticed that exposure to sunlight dramatically improved cutaneous skin lesions caused by a tuberculosis infection (lupus vulgaris) and received the Nobel Prize in 1903 for his enlightening observations. This led to the use of solariums with UVB radiation as a way to treat patients with tuberculosis and gave rise to the use of heliotherapy to improve health (Holick & Jung, 1999). The principal beneficial effect of sun exposure is its role in the production of vitamin D in the skin and it's essential for healthy bone growth and maintenance (Holick, 2004; Sivamani, Crane, & Dellavalle, 2009; Webb, Decosta, & Holick, 1989; Wolpowitz & Gilchrest, 2006). Naturally occurring vitamin D is very rare in a human diet, it is present mainly in fatty fish and cod liver oil. However, short periods of midday sun exposure will produce sufficient vitamin D, and prolonged sun exposure will not provide additional benefits (www.who.int/uv/faq/uvhealtfac/en/). It has been suggested that one full body UV exposure causing a slight pinkness in skin (one minimum erythemal dose, 1 MED) is equivalent to an oral intake of somewhere in the range 250–625 µg (10,000–25,000 IU) of vitamin D₃ (Engelsen, 2010). Additional studies supported the theory that one full-body exposure to sunlight can be equivalent to an oral vitamin D intake of 250 µg (10,000 IU) (Vieth, 1999). It has been suggested that the increase in serum 25(OH)D attained from exposure to UVB radiation is often more effective than ingesting 1000 IU vitamin D₂ or vitamin D₃ daily (Buettner & Raasch, 1998).

Since it takes approximately 8 h for previtamin D₃ in the skin to fully convert to vitamin D₃ and it takes additional time for the vitamin D₃ to enter the dermal capillary bed this is at least two of the explanations for why it was observed that vitamin D₃ produced in the skin last 2–3 times longer in the circulation when compared with oral consumption (Haddad, Matsuoka, Hollis, Hu, &

Wortsman, 1993) Furthermore, when vitamin D₃ is produced in the skin 100% of it is potentially bound to the vitamin D binding protein. When vitamin D₃ is consumed in the diet or in a form of supplement it gets combined to chylomicrons which are transported into the lymphatic system and then into the venous system where approximately 60% of the vitamin D₃ is bound to the vitamin D binding protein and 40% is rapidly cleared in the lipoprotein bound fraction (Haddad et al., 1993). Therefore, UVB is the most important for vitamin D production and lower vitamin D status is a marker for reduced sun exposure (Baggerly et al., 2015).

There is increasing evidence that sunlight and vitamin D are linked to reduced cancer risk (Holick, 2014). Epidemiologic and ecological studies have suggested that living at higher latitudes and having lower blood levels of 25-hydroxyvitamin D are associated with increased risk for up to 15 types of cancers including breast, colon, lung, lymphoma, pancreatic, ovarian and prostate cancer (Grant et al., 2015; Holick, 2014). Other diseases caused (partially) by insufficient vitamin D or insufficient sunlight include diabetes, multiple sclerosis and heart disease (Grant, 2006; Holick, 2004; Lips, van Schoor, & de Jongh, 2014; Sivamani et al., 2009). A possible relationship between vitamin D and blood pressure was reported by Rostand et al 1997. The results showed an inverse relationship between UV light and the prevalence of hypertension (Pilz, Tomaschitz, Ritz, & Pieber, 2009; Rostand, 1997). Further, it has been suggested that UVB (not UVA) light is linked to reduced blood pressure (Liu et al., 2014). Hyppönen et al reported that children who received 50 µg (2,000 IU) of vitamin D in the first year of life had 78% lower risk of developing type I diabetes (Hyppönen, Läärä, Reunanen, Järvelin, & Virtanen, 2001). In 1981, R. Edgar Hope-Simpson proposed that a 'seasonal stimulus' closely associated with UV radiation explained the remarkable seasonality of prevalent influenza. Vitamin D deficiency is common in the winter, and activated vitamin D, 1,25(OH)₂D, has profound effects on human immunity. An interventional study showed that vitamin D reduces the occurrence of respiratory infections in children. It was concluded that vitamin D, or lack of it, may be Hope-Simpson's 'seasonal stimulus' (Aloia & Li-Ng, 2007; Cannell et al., 2006). These and other benefits of sun exposure led to a suggestion that the cardiovascular and other health benefits of UVB and vitamin D may outshine the risks of skin cancer. However, the WHO recommends small amounts of UV as essential for the production of vitamin D in humans, yet prolonged human exposure to solar UV radiation may result in acute and chronic health effects on the skin, eye and immune system.

Figure 4 A Schematic Representation of the Major Causes for Vitamin D Deficiency and Potential Health Consequences.



Note 3 This figure is reproduced from (Holick, 2010)

1.4.1.1 UV exposure, vitamin D and mental health

Convergent evidence from epidemiology, basic neuroscience, experimental animal models and clinical trials now connects low vitamin D status with an increased risk of a wide range of neurological and psychiatric disorders. Research demonstrates that the timing of exposure to low vitamin D influences the nature of brain phenotypes, as exposures during gestation versus adulthood result in different phenotypes. With respect to early life exposures, there is robust evidence from rodent experiments indicating that transient developmental vitamin D (DVD) deficiency is associated with changes in brain structure, neurochemistry, gene and protein expression and behaviour (Cui et al., 2014; J. J. McGrath, Burne, et al., 2010). In particular, DVD deficiency is associated with alterations in the dopaminergic neurotransmitter systems (Cui et al., 2014). In contrast, recently published animal experiments indicate that adult vitamin D deficiency

is associated with more subtle neurochemical and behavioural phenotypes. Several studies have proposed functions for vitamin D in both in the developing (D. Eyles, Brown, Mackay-Sim, McGrath, & Feron, 2003) and adult brain (Garcion, Wion-Barbot, Montero-Menei, Berger, & Wion, 2002; J. McGrath, 1999). It has been suggested that low levels of Vitamin D during early life may be relevant to several brain diseases such as schizophrenia (J. J. McGrath, Burne, et al., 2010). Schizophrenia has been associated with inadequate sun exposure and vitamin D deficiency and it is more common in the Scandinavian countries (Kinney et al., 2009).

Furthermore, vitamin D has been associated with several psychiatric and developmental disorders (depression, schizophrenia, Autistic Spectrum Disorder) (Berk et al., 2007; Humble, 2010; Schneider, Weber, Frensch, Stein, & Fritze, 2000). In a systematic review on the relationship between vitamin D deficiency and depression the authors concluded that, in a community setting, depressed adults had significantly lower serum concentrations of vitamin D than those without depression (Anglin, Samaan, Walter, & McDonald, 2013).

1.4.2 Omega 3 and its effects on general and mental health

Association of omega 3 (ω -3) consumption and certain diseases has been investigated especially in malnourished populations (consuming little ω -3). Research revealed significant relationship between ω -3 intake and heart disease, cancer (some cancer protective properties of omega-3) and diabetes mellitus (Karr et al., 2011). One study showed that individuals with a typical Mediterranean diet (rich in fish intake) performed significantly better on cognitive tasks than individual consuming less PUFA. The literature suggests some protective qualities of omega-3 consumption, especially with relation to cognitive decline (Karr et al., 2011; Anett Nyaradi et al., 2013). Morris and colleagues (2003) reported effectiveness of ω -3 PUFA in treatment of Alzheimer disease and age related cognitive decline (Morris et al., 2003).

There is some evidence for reduction in PUFA levels in patients with schizophrenia (Yao et al, 1994; Berger et al, 2006) and major depressive disorder (Peet et al, 1998). Dietary deficiency of omega-3 fatty acids in humans has been related to increased risk of some mental disorders, including attention-deficit disorder, dyslexia, dementia, depression, bipolar disorder and schizophrenia (Adams, Lawson, Sanigorski, & Sinclair, 1996; Freeman et al., 2006; Gómez-Pinilla, 2008; Peet, Murphy, Shay, & Horrobin, 1998). As mentioned before, folate and choline have a role in the closure of the fetal neural tube and prenatal folate deficiency causes neural

tube defects (NTD). The Californian mothers' cohort study reported an increased risk of neural tube defects of their children with lower maternal choline intake (Shaw et al, 2004). The important finding of the negative effects of folate deficiency has led to worldwide fortification of foods with folate to prevent deficiency in pregnant women. Vitamin B12 has also been identified as an important nutrient for fetal development. One Chinese study showed that lower maternal levels of both folate and B12 significantly increased the risk of having a child with a NTD (Zhang et al, 2009).

Examining the research evidence on the relationship between nutrition and psychosis, evidence is limited and inconclusive. Studies have found that functional deficiencies or imbalances in certain fatty acids may contribute to a wide range of developmental and psychiatric conditions, including dyslexia, dyspraxia, and attention deficit hyperactivity disorder (ADHD), autism, depression, bipolar disorder and the schizophrenia spectrum (Karr et al., 2011). This is important especially at early age of development where research indicated that poor maternal nutrition during pregnancy is associated with lower cognitive functions and can lead to psychotic symptoms in their offspring (Hedelin et al., 2010). Further, a low maternal fatty acids intake during pregnancy is found to increase the risk for lower IQ and suboptimal neuro-developmental outcomes in childhood, factors that in turn are associated with an increased risk of adult mental disorder like schizophrenia (Hibbeln et al., 2007), for example, some studies reported significantly lower level of PUFA in patients with schizophrenia (Berger, Smesny, & Amminger, 2006). Based on limited and mixed results, it is important to further investigate the relationship between prenatal omega 3 intake and its impact on the offspring cognitive development which in turn is associated with later mental health problems such as schizophrenia ((Berger et al., 2006).

Chapter 2 Methodological Innovations

Here I describe several novel approaches and advanced statistical methods that I applied in my thesis.

2.1 Comprehensive Meta-Analysis

In this thesis, in chapter 3, I addressed the role of prenatal fish oil intake on childhood cognitive abilities using the Comprehensive Meta-Analysis software (CMA) version 3.0 (<https://www.meta-analysis.com>). In short, a meta-analysis method offers techniques to assist when combining results from different studies (Borenstein, Hedges, Higgins, & Rothstein, 2009). A meta-analysis is an important technique especially in situations when there is heterogeneity and inconsistencies in the different studies. By relating the study outcome to a variable available from several studies, $outcome = b + b \cdot X$, a meta-regression can give better understanding of potential factors contributing to study differences.

As for the CMA itself, the advantages of this particular software is its flexibility in working with many different sorts of data, its simplicity of use and its ability to customise and export forest plots. This version of CMA includes 100 formats for data entry and advanced computational options such as subgroup analysis, meta-regression and procedures to assess publication bias (Borenstein, Hedges, Higgins, & Rothstein, 2009). A typical drawback of meta-analyses approach is its retrospective nature since all analyses has been done already and adoption has to be made accordingly.

2.1.1 Pooling results from randomised control trials and observational studies

Randomized controlled trials (RCT) are described as the gold standard in the hierarchy of research designs for evaluating the efficacy and safety of a treatment intervention. However, their results can have limited applicability to patients in clinical settings (Silverman, 2009). Observational studies using large health care databases can complement findings from randomized controlled trials by assessing treatment effectiveness in patients encountered in day-to-day clinical practice. Results from these designs can expand upon outcomes of randomized controlled trials because of the use of larger and more diverse patient populations with common comorbidities and longer follow-up periods. Furthermore, well-designed observational studies can identify clinically important differences among therapeutic options and provide data on long-term drug effectiveness and safety. However, they cannot rule out the possibility that the association

was caused by a third factor linked to both intervention and outcome (a confounder). In contrast, random allocation in RCTs ensures no systematic differences between intervention groups in factors, known and unknown, that may affect outcome. Double blinding ensures that the preconceived views of subjects and clinicians cannot systematically bias the assessment of outcomes (Sibbald & Roland, 1998). Observational studies cannot replace trials, nor do trials make observational studies unnecessary. Both designs are susceptible to particular bias, so neither provides perfect information (Sørensen, Lash, & Rothman, 2006). In this thesis I addressed the inconclusive results that come from both observational studies and randomized control trials by integrating study results. A systematic review and Meta-Analysis of combined results from RCTs and observational studies may be the next step towards understanding and estimating the association between maternal n-3 PUFA levels and childhood neurodevelopment, the topic introduced in chapter 3 of the thesis.

2.1.1.1 Converting from the log odds ratio to d

Meta-analysis is now used extensively in reviews of randomized controlled trials and observational studies, but the problems include how to compare non-identical outcomes. The following section explains the method used to convert from a log odds ratio (LogOR) to the standardized mean difference (SMD). This method was used in instances where studies reported different metrics and we needed to convert them to a common index before we could proceed with the synthesis. This simple method for converting an odds ratio to effect size explained here enables reviewers to maximize the information available.

We used a basic method proposed by Hasselblad and Hedges (1995) to convert dichotomized outcome into continuous outcomes. Also variations of the method have been proposed by Sanchez-Meca, Martin-Martinez, & Chacon-Moscoso, 2003; Whitehead, 2002. The conversion method by Hasselblad and Hedges allows the direct conversion of odds ratios into SMDs. The method is based on the assumption that mean scores in each group follow a logistic distribution (i.e. a near normal distribution) and that variances are equal between groups. The basic formula is:

$$\text{SMD} = \text{LogOR} \times \sqrt{3/\pi}$$

where π is the mathematical constant (approximately 3.14159).

2.1.2 The concept of multiple outcomes analysis

In the meta-analysis presented in this thesis, the studies reported data on more than one cognitive outcome, where the different outcomes are based on the same participants. Normally, separate meta-analyses would be performed, one using data for one outcome and the other using the data for another outcome etc. The Comprehensive Meta-Analysis software used to perform my meta-analyses allows to incorporate all outcomes in the same analysis, meaning, we computed a summary effect for overall cognitive abilities which combines the data from all reported specific cognitive domains. The software takes into account that the data for specific cognitive abilities are not independent of each other and thus the errors are correlated (Borenstein et al., 2009). In general, treating each specific cognitive domain reported within one study as a separate study and performing a meta-analyses with multiple studies could be problematic (computing the summary effect across studies). This approach would assign more weight to studies with multiple outcomes than to studies with only one outcome. Further, this approach would lead to an incorrect estimate of the precision of the summary effect because it would treat specific domains as providing independent information and as we would assume the specific cognitive domains come from the same set of participants and are not independent of each other (Borenstein et al., 2009; Cooper & Hedges, 2009). Normally, the effects that one would like to combine are positively correlated therefore this method would tend to underestimate the error of the summary effect. A synthetic effect size for each study is created in order to compute a summary effect using multiple outcomes defined as the mean effect size in that study. This includes a variance that takes account of the correlation among the different outcomes. This effect size and variance is used to compute a summary effect across studies. Higher correlations yield less precise estimates of the summary effect.

2.2 Quantile regression

In statistics, regression is a common method used to obtain a summary of the relationship between a response variable y and a set of covariates x . For instance, a least squares regression captures how the mean of y changes with x of the outcome. Epidemiological research often focuses on inference for high or low values in a population distribution, e.g. high body mass index, low birth weight, high blood pressure. However in some instances, a single mean curve might not be informative enough particularly if the primary interest resides in the tail ends of the distribution. While linear regression speculates the question 'What is the relation between X and Y ?' quantile

regression extends this to, 'For whom does a relation between X and Y exist' as well as testing for whom a relation is stronger or weaker" (Petscher & Logan, 2014). Quantile regression, as introduced by Koenker and Bassett (1978), is a method for estimating functional relations between variables for all portions of a probability distribution (Koenker & Bassett, 1978). Further, a set of equally spaced quantiles (e.g. every 5% of the population) can define the shape of the distribution in addition to its central location. Thus, conditional quantile functions provide a more complete view. There are various reasons as to why one would choose to perform quantile regression, for example, when the distribution of y might be asymmetric around the mean or heteroscedasticity might exist in the data (Cade & Noon, 2003; McGreevy, Lipsitz, Linder, Rimm, & Hoel, 2009). For example, regression models with heterogeneous variances, which are common in epidemiological studies, imply that there is not a single rate of change that describes changes in the probability distributions, therefore, focusing only on changes in the means might underestimate, overestimate, or fail to distinguish real nonzero changes in heterogeneous distributions (Cade & Noon, 2003).

I used quantiles to describe the distribution of the dependent variables. Quantiles and percentiles are synonymous where, for example, the 0.99 quantile would be the 99th percentile. The best known quantile is the median that is the 0.50 quantile. One practical consideration is that the distribution of the dependent variable is particularly important and that needs to be continuous with no zeros or too many repeated values.

Unlike interpretation of linear regression, the interpretation of the quantile regression results need to specify which quantile of the dependent variable they refer to.

There are numerous advantages of using the quantile regression. First of all, its flexibility for modelling data with heterogeneous conditional distribution. Secondly, the median regression is more robust to outliers than the normal linear regression. Finally, the greatest advantage is that it has richer description of the data, it can show different effects of the independent variables on the dependent variables depending across the spectrum of the dependent variable.

Since the data used for analysis in chapter 4 was highly skewed, we used analysis based on quantile regression (the data and statistical analysis are further explained in Chapter 4, methods section).

2.3 Missing data

Missing observations caused by dropouts or uncompleted responses might cause a problem in studies of longitudinal data. When the analysis is restricted to complete cases and the missing data depend on previous responses, the generalized estimating equation (GEE) approach, which is commonly used when population-averaged effects are of primary interest, can lead to biased parameter estimates. There are also different approaches to address such problem, i.e. Multiple Imputation (Little & Rubin, 1987) or Multiple Imputation by Chained Imputation (White, Royston, & Wood, 2011). However, if only a relatively small proportion of the data contain missing values the records containing missing data can be deleted using only the complete cases in the analyses. Further, in the statistical literature missing data are usually classified according to the underlying reasons of being missing. If data is missing completely at random (MCAR), the probability of a value being missing is independent of both the observed data and the unobserved data, e.g. by tossing a dice, comparisons are generally not subject to bias. When, in a function $Y = f(X)$ relating an outcome with exposure X , the probability of a particular value y being missing depends only on the observed data (Y or X), then the missing data is considered to be missing at random. If the missing data can be considered missing at random, the estimates obtained for the quantile regression, are unbiased. If this assumption is false, the missing data are not ignorable and the missing mechanisms should be modelled (Little & Rubin, 1987).

In the work presented here using the large cohort of Swedish women the data used are essentially complete. Inverse-probability weighting (IPW) is more sophisticated method for handling missing data, which make the weaker assumption that the data are missing at random. We will apply this method to determine whether this method changes the conclusions of the original analysis.

2.4 Data sources

Apart from the Meta-Analysis, the data used for analysis in chapter 4 and 5 come from the Swedish Women's Lifestyle and Health (WLH) cohort initiated in 1991 in Sweden. Detailed description of the Swedish cohort is provided in chapter 4 of this thesis.

2.5 Statistical sources

In this thesis I used two different statistical software. For the Meta-Analysis I used the Comprehensive Meta-Analysis Software version 3 which I briefly described in section 2.1.

The SAS software version 9.3 was used for studies included in chapter 4 and chapter 5. All of the statistical graphs and figures were produced using the SAS/GRAPH software. The QUANTREG procedure in the SAS software was used for the quantile regression models in the sun exposure and psychotic symptoms study. The LOGISTIC procedure was used for the sun exposure and depressive symptoms study in chapter 5.

This thesis is written using the Word 2013. The references were managed using the open source Mendeley Desktop 1.15 software (<https://www.mendeley.com>).

2.6 The main objectives of the PhD project

Recently, nutrition is gaining recognition as a potential environmental factor contributing to development of mental illness and moderating symptom severity. Research on nutrition and cognitive development, and psychiatric morbidity is limited and often inconsistent. The primary objective of the current PhD project is to conduct a rigorous evaluation of the association between dietary behaviour across critical periods of development and cognitive functions, psychosis and depression. The previous reports from Meta-Analysis published conflicting results. The research evidence from observational studies suggests that nutrients may play an important role in the cognitive development of children whereas results from RCTs are inconclusive and show less effect. In order to settle inconsistencies and conflicting results within and between the impacts of PUFA (fish oil) supplements/fish consumption in pregnancy on childhood cognition and behaviour, an intensive and careful systematic review and Meta-Analysis of epidemiological studies and RCTs is needed. In order to meet the objective the present study will look at the nutrition intake prenatally (Chapter 3) and for this reason a systematic review and Meta-Analysis of epidemiological studies and RCTs on PUFA supplements in pregnancy, and childhood cognition and behaviour will be conducted. I extracted more detailed data than previous reports focusing on specific domains of cognition, including Intelligence, language abilities, motor skills, memory, and reasoning, and examine the current evidence more specifically. By doing this the present research/evaluation can contribute to develop new concepts/hypothesis on the role of nutrition in general and specific neuropsychological functions in children.

In the next sections, using the data from the Swedish Women Health Study (Roswall, Sandin, Adami, & Weiderpass, 2015), I looked at the link between sun exposure behaviours and vitamin D, and psychotic (Chapter 4) and depressive (Chapter 5) symptoms in adulthood. We examined further impact of nutrients on possible psychotic and depressive symptoms. The objective is to

look not only at PUFAS intake but also to investigate vitamin D (sun exposure behaviours) and the longitudinal relation between their exposure and psychotic and depressive symptoms in adults. This research will provide new and robust evidence for the ongoing debate on the role of nutrition through the lifespan as a possible risk factor for cognitive impairment and psychiatric illnesses. The Swedish Women's Lifestyle and Health cohort provides an opportunity to address these questions due to its detailed individual data on solar UV exposure in different periods of life.

Chapter 3 Fish Oil and Fish Intake during Pregnancy and Cognitive Functioning In Offspring: Systematic Review and Meta-Analysis of Randomised Control Trials and Observational Studies

3.1 Summary

The main objective of this chapter was to examine the effect of maternal fish oil intake and fish oil supplementation on offspring cognitive abilities by performing meta-analyses of randomized controlled trials and observational studies. PubMed, the Cochrane Library, ClinicalTrials.gov and reference lists were used to search for relevant studies. The Meta-Analysis included 8 randomized controlled trials that reported prenatal fish oil supplementation vs placebo and any cognitive outcomes in their children (average age 3 years old), and 5 observational studies that reported prenatal consumption of oily fish by pregnant women and any cognitive outcome of their children (average age 4.5 years old). The total number of participants in the RCTs was $n=1,433$ and in the observational studies $n=16,391$. The randomized controlled trials indicated better cognitive abilities in children of mothers in the fish oil supplementation group. For the measure of overall cognitive ability the standardized difference in means (SMD) was estimated to 0.10 (95% CI, -0.01 to 0.20; $p=0.07$) and for memory functions the SMD was 0.21 (95% CI, 0.01 to 0.41; $p=0.04$). The observational studies showed better overall cognitive ability with a pooled OR of 1.92 (95% CI, 1.61 to 2.30; $p<0.001$) and for the domain of language and verbal skills the OR was 1.93 (95% CI, 1.37 to 2.73; $p<0.001$) among children of mothers consuming 2 to 3 fish servings per week

during pregnancy. Maternal intake of fish oil during pregnancy is associated with improved cognitive abilities in the offspring. Specifically, fish oil is associated with advancement in language and memory abilities.

3.1 Introduction

Cognition represents a complex set of higher mental functions sub-served by the brain, and includes attention, memory, thinking, learning, and perception (Bhatnagar & Taneja, 2001). The literature suggests that cognitive development in children greatly depends on prenatal nutrition particularly in the third semester when the brain development begins. Omega-3 polyunsaturated fatty acid PUFA is a main component of the brain cell membrane and is critical for optimal brain development (Karr et al., 2011). While for some nutrients, absence may have no effect, for fatty acids this absence will have a negative effect. Particularly, brain function is critically dependent on the intake of the essential fatty acids that cannot be synthesized by the human body and can only be obtained from the diet. The requirements during pregnancy have not been well established, however, ISSFAL (the International Society for the Study of Fatty Acids and Lipids) has recommended 300 mg DHA daily as a minimum dosage for pregnant women (<http://www.issfal.org/statements/adequate-intakes-recommendation-table>).

DHA (Docosahexaenoic acid) is the principal omega-3 (n-3) long-chain polyunsaturated fatty acid (LCPUFA). DHA is the end-product of the n-3 series, and is the predominant fatty acid of membrane phospholipids in the brain grey matter and in the retina of mammals (Guesnet & Alessandri, 2011). The time of the most rapid neural development occurs in the second half of pregnancy, mainly during third trimester. On this basis, supplementation of the maternal diet with omega-3 fatty acids, especially DHA, later in pregnancy is thought to be especially important (Jensen, 2006).

Oily fish contains high concentrations of omega-3 polyunsaturated fatty acids. Several observational studies reported that consumption of oily fish (salmon, mackerel, sardines, and trout) may be beneficial for cognitive development of the offspring. (Daniels et al., 2004; Gale et al., 2008; Hibbeln et al., 2007; Oken & Bellinger, 2008) . There have been RCTs designed to assess the cognitive effects of omega-3 through the intake of fish oil but the results have been mixed (Campoy et al., 2011; Dunstan, Simmer, Dixon, & Prescott, 2008; Helland et al., 2008; Judge, Harel, & Lammi-Keefe, 2007; Makrides et al., 2010). Thus, integration of study results and careful examination of potential sources of heterogeneity is necessary.

To date there is no published Meta-Analysis evaluating both RCTs and observational studies on maternal PUFAs intake and child's neurodevelopment. A Meta-Analysis published in 2013 included only RCT designs and did not find any difference on cognitive abilities (including Developmental Standard Scores, IQ, and motor or language development) between the LCPUFA-supplemented and control groups (Gould et al., 2013). Eleven RCTs were included in the review. Most trials had methodologic limitations. No differences in standardized psychometric test scores for cognitive, language, or motor development were observed between the LCPUFA-supplemented and control groups, except for cognitive scores in 2-5-y-old children, in whom supplementation resulted in higher Developmental Standard Scores (mean difference: 3.92; 95% CI: 0.77, 7.08; $n = 156$; $P = 0.01$). However, this effect was from 2 trials with a high risk of bias. However the evidence did not conclusively support or refute the possible positive effects of omega-3 supplementation in pregnancy on cognitive outcomes.

The inconclusive results might be due to methodological limitations. Most RCTs only had a small or medium sample size, having low statistical power. Pooling of data using meta-analytic methods allows increasing statistical power. Cognition is a multi-dimensional construct consisting of both general ability such as IQ, and specific cognitive abilities: memory, executive functions, and language. Different abilities are supported by different brain networks, but these have not been studied separately in detail. Animal studies have reported that n-3 deficiencies result in behavioural impairments observed in spatial learning, increased and disrupted motor activity and other learning tasks (de Souza et al., 2011).

The objective of this Meta-Analysis is to test if maternal prenatal intake of fish oil is associated with offspring cognitive abilities. In particular, general as well as specific cognitive functions in both randomized controlled trials (RCT) and observational studies (OS).

We hypothesized that better cognitive outcome will be present in children of mothers who consumed fish oil during pregnancy, particularly in specific cognitive outcomes.

3.2 Methods

3.2.1 Inclusion and exclusion Criteria

We included

1. All observational studies that present information on pregnant women's fish intake and its effect on cognitive abilities of their offspring (including general cognitive abilities, IQ, motor skills, language, memory, reasoning)
2. All RCTs that investigated the effects of fish oil supplementation during pregnancy on child cognitive abilities (including general cognitive abilities, IQ, motor skills, language, memory, and reasoning)

We excluded

1. Studies reporting further offspring supplementation, and physical (but not mental) development
2. Studies not written in the English language
3. Studies not reporting cognitive outcomes

3.2.2 Literature search and selection

The systematic review was planned and reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009)

The medical literature was searched using PubMed, the Cochrane Library, ClinicalTrials.gov and reference lists.

Studies on prenatal fish oil intake and children cognitive abilities were identified using the terms "nutrition" together with "pregnancy" and "cognition"

Search details through PubMed MESH search:

("nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR "nutrition"[All Fields] OR "nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]) AND ("cognition"[MeSH Terms] OR "cognition"[All Fields])

Database search was completed by a researcher (IP). Studies were assessed against the inclusion criteria by the researcher (IP), first using the titles, then using the abstracts, and finally using the full text.

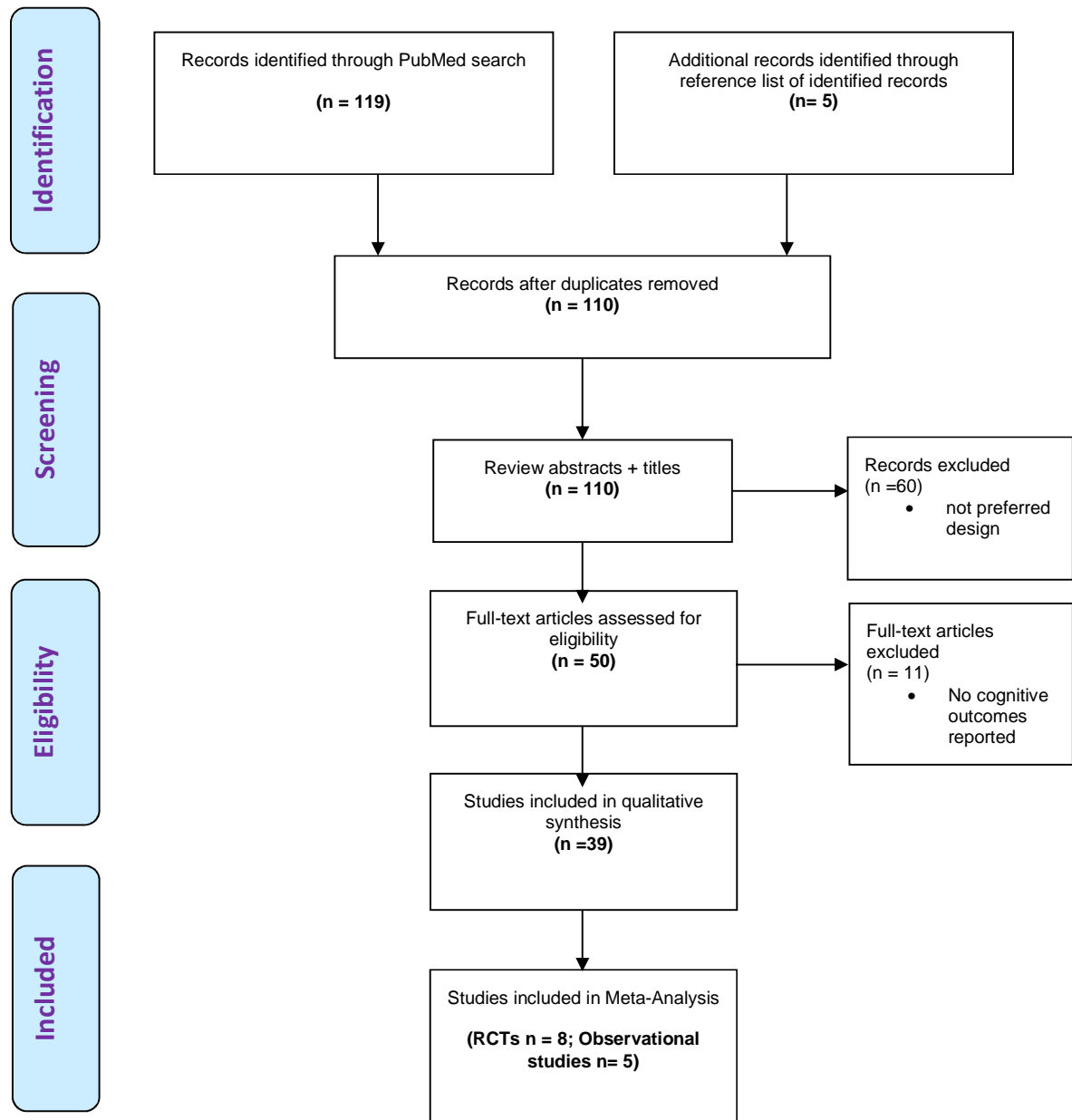
A total of 8 randomized controlled trials; (Campoy et al., 2011; Dunstan et al., 2008; Helland et al., 2008; Helland, Smith, Saarem, Saugstad, & Drevon, 2003; Judge et al., 2007; Makrides et al., 2010; Meldrum, Dunstan, Foster, Simmer, & Prescott, 2015; Tofail et al., 2006) and 5 observational studies that met our inclusion criteria were found (Daniels et al., 2004; Gale et al.,

2008; Hibbeln et al., 2007; Mendez et al., 2009; Oken & Bellinger, 2008). The summary estimate was based on the reported means and standard deviation, sample size or odd ratios (ORs) and 95% confidence intervals (CIs). We also contacted the authors of the papers in case of missing mean values for cognitive outcomes (Gale et al., 2008; Oken & Bellinger, 2008).

Studies included in this review were randomized controlled trials (RCTs) and observational studies in humans, with English-only text, with no limitations set for date of publication. The last search was completed in March 2015. The review author (IP) assessed the titles, abstracts and the full text of the article for study eligibility. Additionally, reference lists of selected articles were searched for citations according to the inclusion criteria. We excluded studies with infant supplementation and studies that did not reported cognitive measures.

Predefined cognitive outcomes (intelligence, language, motor skills, memory, and reasoning) were extracted blindly by the first author according to the available cognitive outcomes in included studies. The authors (IP, AR) assessed the outcome measures and reclassified the cognitive outcome where needed.

Flow Diagram



3.2.3 Measurements and variables

Measurements and variables included in the present meta-analysis are listed in **Table 2** in results section. We included the cognitive domain variables: general intellectual ability (IQ), language, motor skill, memory and reasoning.

Demographic characteristics, study duration, dosage and dropout rates were first extracted. The core data in each RCT study consisted of the sample size, the mean values of relevant continuous cognitive variables and their SDs in the placebo and treated groups. When this information was not available, instead we extracted the sample size for each treated and placebo group, mean value and the corresponding *P* value of the statistical test used to estimate the standardized mean difference.

From the observational studies we extracted OR and confidence limits.(Daniels et al., 2004; Hibbeln et al., 2007; Oken & Bellinger, 2008) In the observational studies where the ORs were not available we instead extracted means and standard errors and number of participants for each group (fish intake 2 to 3 times per week vs no fish intake).(Gale et al., 2008; Mendez et al., 2009; Oken & Bellinger, 2008) As comparison to the women who did not consume any fish we decided to compare the most commonly reported frequency of fish intake which was 2 to 3 servings/week.

3.2.4 Quality assessment of the included clinical trial

All RCTs were double-blinded in this review however none of the RCTs described blinding methods. Except for 1 study (Judge et al., 2007) all provided a description of an account of all participants (**Table 1**).

Table 1 The Jadad scale for quality review of randomized controlled trials.

Source	Randomization mentioned (1 point)	Randomization method described & appropriate (1 point)	Inappropriate randomization (-1 point)	Double blind (1 point)	Double blinding described & appropriate (1point)	Inappropriate blinding (-1 point)	Description of withdrawals & dropouts (1 point)	Total score (Max 5points)
Judge et al 2007	1			1				2
Campoy et al 2011	1	1		1			1	4
Makrides et al 2010	1	1		1			1	4
Helland et al 2003	1			1			1	3
Helland et al 2008	1			1			1	3
Tofail et al 2006	1			1			1	3
Dunstan et al 2006	1	1		1			1	4
Meldrum et al 2015	1	1		1			1	4

Note 4 Scoring of items: each item was given a score of 1 point for each 'yes' or 0 points for each 'no'. There were no in-between mark

3.2.5 Additional data

The authors of three included studies where some cognitive outcomes were missing (Gale et al., 2008; Hibbeln et al., 2007; Oken & Bellinger, 2008) were contacted and the information was provided via email (table of means provided by Gale et al).

3.2.6 Statistical Methods

From the extracted data we calculated the pooled effect size in the form of SMD (standardized mean differences) for RCTs and two OS, and the pooled odd ratios for the remaining OS separately. All analyses were performed using the Comprehensive Meta-analysis version 3 software package (www.meta-analysis.com). Comprehensive Meta-analysis version 3 includes a module that enables the analysis of multiple outcomes from the same study. For example, multiple outcomes analysis allows including effects of several outcomes accounting for correlation among the different outcomes whereas the same participants and the information for the different effects are not independent from each other. This module was used to derive an estimate for the overall cognitive outcomes. Heterogeneity among study point estimates was assessed with Q statistics with magnitude of heterogeneity being evaluated with the I^2 index. Weighted mean effect sizes were computed under both fixed- and random-effects meta-analytic assumptions; homogeneity analyses (Q and I^2) followed fixed-effects assumptions for combined analysis and random effects models for multiple outcomes analysis. Meta-regression was used to assess the effects of potential moderators.

3.2.7 Statistical analysis – randomised control trials

The first step involved calculating for each cognitive domain and each study the effect sizes for the difference between supplemented and placebo groups, including intelligence, language, motor skills, memory, and reasoning. We analysed differences between the fish oil group vs placebo group for each cognitive domain group separately. Overall cognitive abilities were also considered by analysing the difference between the fish oil vs placebo for combined cognitive outcomes using the multiple outcomes module.

3.2.8 Statistical analysis - Observational studies

The first step involved calculating for each cognitive domain and each study the effect sizes for the difference between women who reported fish consumption and women with no fish

consumption, including intelligence, language, motor skills, memory, and reasoning. The meta-analysis analysed differences between the fish consumption group vs no consumption group for each cognitive domain group separately. Overall cognitive abilities were also considered by analysing the difference between the two groups for overall cognitive outcomes using the multiple outcomes module.

3.2.9 Moderator analysis

Potential sources for study heterogeneity were examined using meta-regression analysis. Meta-regression was performed under the random effect model in order to test the impact of two covariates separately. We included initial DHA prenatal dose (mg/week) (RCTs), and child's age (in months) at study inclusion (observational studies) as potential moderating variables.

3.2.10 Sensitivity analysis

We assessed publication bias with Begg's funnel plot and Egger's test. If publication bias exists, the Begg's funnel plot is asymmetric or the Egger's test P value is <0.05. In this way, we assessed whether there was a tendency for selective publication of studies based on the nature and direction of their results.

In addition, we used the fail-safe procedure to generate the number of unpublished studies that would be needed to move estimates to a non-significant threshold. To assess the robustness of the results, we performed sensitivity analyses by sequentially removing each study and rerunning the analysis.

We performed Meta-Analysis of observational studies based on the conversion from odd ratios to standardized mean difference. We used a method proposed by (Hasselblad & Hedges, 1995) to convert dichotomized outcome into continuous outcomes. The conversion method by Hasselblad and Hedges allow the direct conversion of odds ratios into SMD. The method is based on the assumption that mean scores in each group follow a logistic distribution (i.e. a near normal distribution) and that variances are equal between groups. The formula is:

$$SMD = \text{LogOR} \times 3\sqrt{\pi}$$
 where π is the mathematical constant (approximately 3.14159).

3.3 Results

Table 2 shows the characteristics of the study populations for both RCTs and observational studies.

Both effect size models, fixed and random, were identical for RCTs ($T^2=0$) therefore for the remainder of this paper, only results of the fixed effects model will be presented.

For observational studies, heterogeneity was not statistically significant, $Q(6) = 4$ ($p=0.19$) and $I^2=34.3$, indicating that 34.3 % of the data variance was due to variation between the studies.

The results were expressed as standardized mean difference (SMD) (for studies reporting mean values), because different instruments were used to measure the cognitive abilities. For observational studies reporting odd ratios the results were expressed as odd ratios.

Table 2 Description of studies that evaluate effects of prenatal fish oil on children cognitive functions.

Author, year of publication	Country	Design	Sample size/characteristics of the mothers of children assessed with cognitive tests	Intervention/Dosage	Follow up/age at cognitive assessment	Outcomes/cognitive measures	Measures selected for Meta- Analysis
Judge et al. 2007	USA	RCT	29 pregnant women aged 18-35 at <20 wk of gestation	214mg of DHA/d from week 24 until delivery or corn oil (placebo)	9 months	Problem solving and recognition memory measured by The Fegan Test of Infant Intelligence	problem solving reclassified as reasoning
Campoy et al. 2011	Multicentre study: Spain Germany and Hungary	RCT	82 pregnant women aged 18-40 at <20 wk of gestation	DHA 500 mg/d or (n=45) placebo/d until delivery	6.5 years	Memory, reasoning and intelligence measured by The Kaufman Assessment Battery for Children	MPC= intelligence; SPS=Memory; SimPS=Reasoning
Makrides et al. 2010	Multicentre study: Australia	RCT	694 pregnant women aged at <21 wk of gestation	(n=351) DHA 800 mg/d or (n=375) placebo (vegetable oil)	18 months	Cognitive and language development measured by The Bayley Scales of Infant and Toddler Development, 3dr Edition	Language, Motor, Cognitive scores as an index for IQ
Helland et al. 2003	Norway	RCT	84 pregnant women aged 19-35 in week 18 of pregnancy	(n=48) DHA 1183mg/d or (n=36) placebo (corn oil)	4 years	Memory, reasoning intelligence and nonverbal abilities measured by The Kaufman Assessment Battery for Children	MPC= intelligence; SPS=Memory; SimPS=Reasoning

Helland et al. 2008	Norway	RCT	143 pregnant women aged 19-35 in week 18 of pregnancy	(n=82) DHA 1183mg/d or (n=61) placebo (corn oil)	7 years	Memory, reasoning intelligence and nonverbal abilities measured by The Kaufman Assessment Battery for Children	MPC= intelligence; SPS=Memory; SimPS=Reasoning
Tofail et al. 2006	Bangladesh	RCT	249 pregnant women Mean age 22.1 at 25 weeks of gestation	(n=125) DHA 1200 mg/d or (n=124) placebo (soy-oil)	10 months	Bayley Scales of Infant Development II which included 2 sub-scales: mental development index and psychomotor developmental index	Mental Development Index for intelligence and Psychomotor developmental index for measures of Motor Skills
Dunstan et al. 2006	Australia	RCT	72 pregnant women at <20 wk of gestation	(n=31) DHA 2200 mg/d or (n=39) placebo (olive-oil)	2.5 years	Griffiths' Mental Development Scale for developmental quotients and Peabody Picture Vocabulary (PPTV) for receptive language	PPTV for language; General quotient score for IQ; Practical reasoning for reasoning and Locomotor for Motor Skills
Meldrum et al, 2015		RCT	72 pregnant women at <20 wk of gestation	(n=25) DHA 2200 mg/d or (n=25) placebo (olive-oil)	12 years	WISC-IV for verbal comprehension, reasoning, working memory, processing speed and full scale IQ abilities	WISC-IV for language, reasoning, memory, intelligence

Gale et al. 2008	UK, Southampton	nonrandomized/cohort design	117 pregnant women aged ≥ 16 years at <17 wk of gestation who completed FFQ	Food Frequency Questionnaire (FFQ) in the 3 preceding months; Fish intake categories: Never (n=62) Less than 1/wk (n=100) and ≤ 1 /wk (n=55)	9 years	The Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) for full scale IQ and Verbal IQ	2 categories of fish intake: Never vs 1/wk or more for measure of IQ
Hibbeln et al. 2007	USA	non-randomised/cohort design	5449 mothers with FFQ reports and cognitive data	FFQ at 32 wk gestation	8 years	IQ measured by the Wechsler Intelligence Scale for Children III (WISC-III)	2 categories of fish intake: None vs >340 g/wk (up to 3 times/wk) for full scale IQ and Verbal IQ
Daniels et al. 2004	UK, Bristol	non-randomised/cohort design	10,092 pregnant women at 32 wk of gestation completed FFQ	FFQ at 32 wk gestation; Fish intake categories: Rarely/Never; 1 meal per 2 wk; 1-3/wk; 4+/wk	15 months and 18 months	MCDI (Vocabulary Comprehension) and DDST (Language)	2 categories of fish intake for Meta-Analysis: Never/Rarely vs 1-3/wk for measures of language (common categories across the selected studies for this Meta-Analysis)
Mendez et al. 2008	Spain	non-randomised/cohort design	392 women at 3 months after delivery completed FFQ on fish intake during pregnancy;	Fish intake categories: ≤ 1 time /wk, $>1-2$ /wk, $>2-3$ /wk, >3 /wk	4 years old	The Spanish version of the McCarthy Scales of Children's Abilities (MCSA) tests (perceptual performance, memory, verbal and motor)	2 categories of fish intake frequency: <1 vs $>2-3$ /wk for scores on Memory, Verbal skills, Motor skills and general cognition as IQ predictor (common categories across the selected

							studies for this Meta-Analysis)
Oken et al. 2008	USA	non-randomised/cohort design	341 mothers reported FFQ	Fish intake at 2nd trimester of pregnancy; Fish intake categories: Never, ≤ 2 , and > 2 times/wk	3 years	PPVT for receptive language and The Wide Range Assessment of Visual Motor Ability (WRAVMA) visual motor skills and fine motor skills (Peabody test)	2 categories of fish intake: Never vs ≥ 2 /wk for scores on PPVT-language and motor skills (Peabody test)

3.3.1 Overall cognitive outcome

Figure 5 presents overall and individual cognitive outcomes results of RCTs for children cognitive abilities after maternal fish oil supplementation. The overall cognitive measures analysis revealed that prenatal fish supplementation (compared with placebo) had an effect size (SMD) of 0.10 (95% CI, -0.01 to 0.2; $p=0.07$) on children cognitive functions.

Figure 6 presents the overall summary effect size (observational studies) for maternal fish intake 2 to 3 times a week vs no fish intake and children cognitive outcomes for studies reporting the odd ratios and mean values. The results are presented separately and were statistically significantly different with pooled odd ratios of OR of 1.92 [95% CI, 1.61-2.30]; $p<0.001$) and approaching statistical significance for OS reporting mean values SMD of 0.22 [95% CI, 0.02 to 0.45]; $p=0.07$).

3.3.2 Intelligence

Only one of eight RCTs reported statistically significant effect for general intelligence (Helland et al., 2003) with a SMD of 0.44, 95% (CI) - 0.01 to 0.88; $p=0.05$. The combined effect for all eight RCTs was not statistically significant for general intelligence. The only data available from observational studies was on verbal intelligence and reported by a single study.(7) The overall effect was statistically significant with OR estimated to 1.92, 95% (CI) 1.72 to 2.71, $p<0.001$.

3.3.3 Language and verbal skills

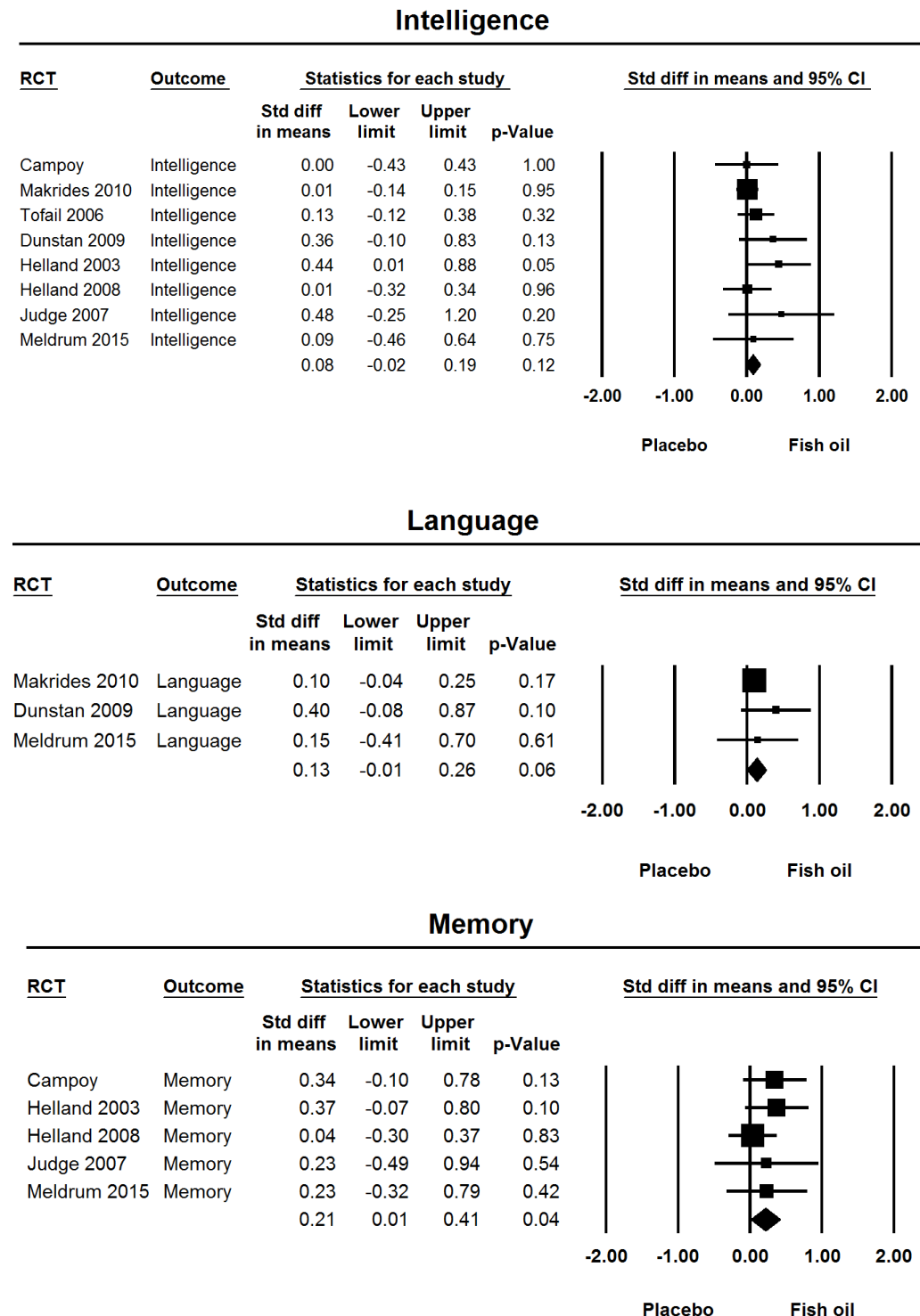
For RCTs, three studies reported data on language domain and the effects were not statistically significant (Figure 5). The combined effect for three RCTs was approaching statistically significant effect with SMD of 0.13, 95% (CI) -0.01 to 0.26, $p=0.06$. Three observational studies reported odd ratios for the verbal skills domain and the results showed statistically significant effect (Daniels et al., 2004 and Oken et al., 2008) OR=1.92, 95% (CI) 1.61 to 2.30, $p<0.001$ and two OS reported mean values for the language domain and the effect was approaching statistically significant results, SMD=0.22, 95% (CI) -0.02 to 0.45; $p=0.07$.

3.3.4 Memory, motor skills and reasoning

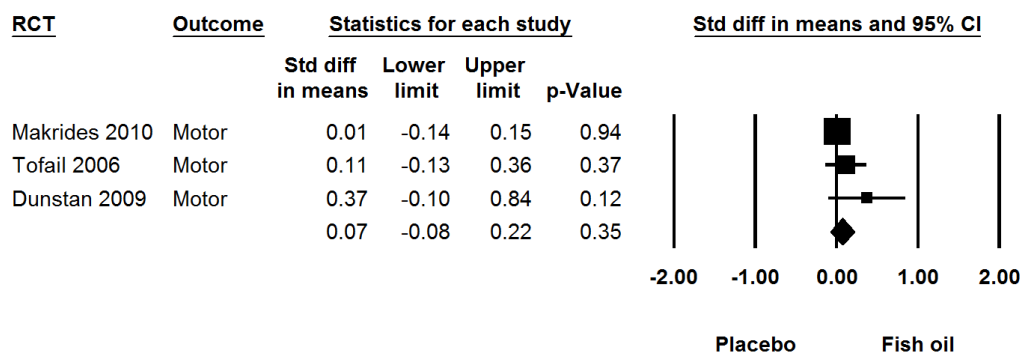
Figure 5 shows statistically significant results in the memory domain for RCTs with an effect size of SMD 0.21 (95% CI, 0.01 to 0.41; $p=0.04$). No data from observational studies was available to estimate an effect for the memory domain.

The remaining analysis on the effects on specific cognitive domains (motor skills and reasoning) revealed no statistically significant results for analysis of either individual or combine cognitive abilities.

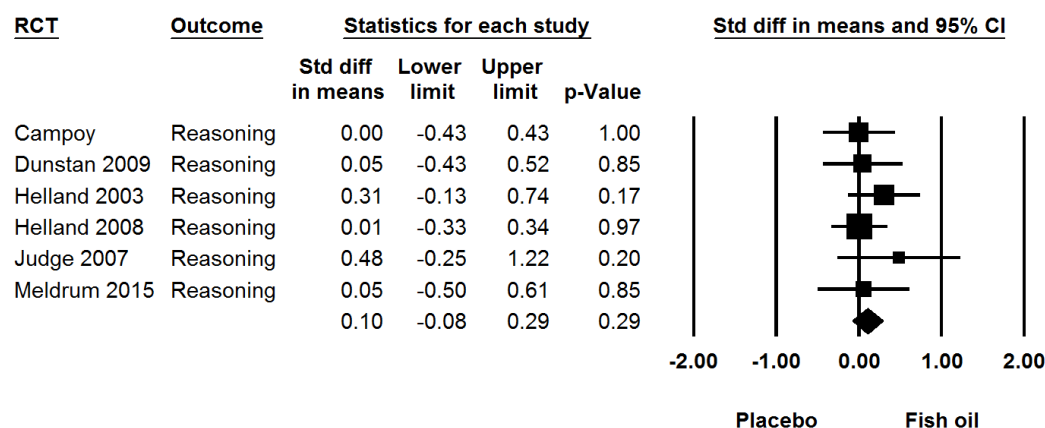
Figure 5 Meta-Analysis of prenatal fish oil supplementation and the effects on overall and specific cognitive abilities of the offspring from eight randomized controlled trials.



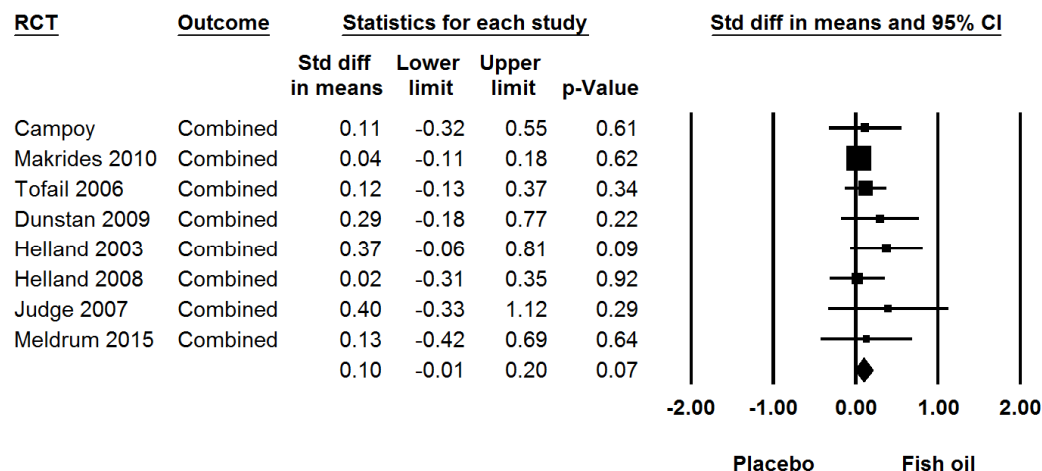
Motor skills



Reasoning

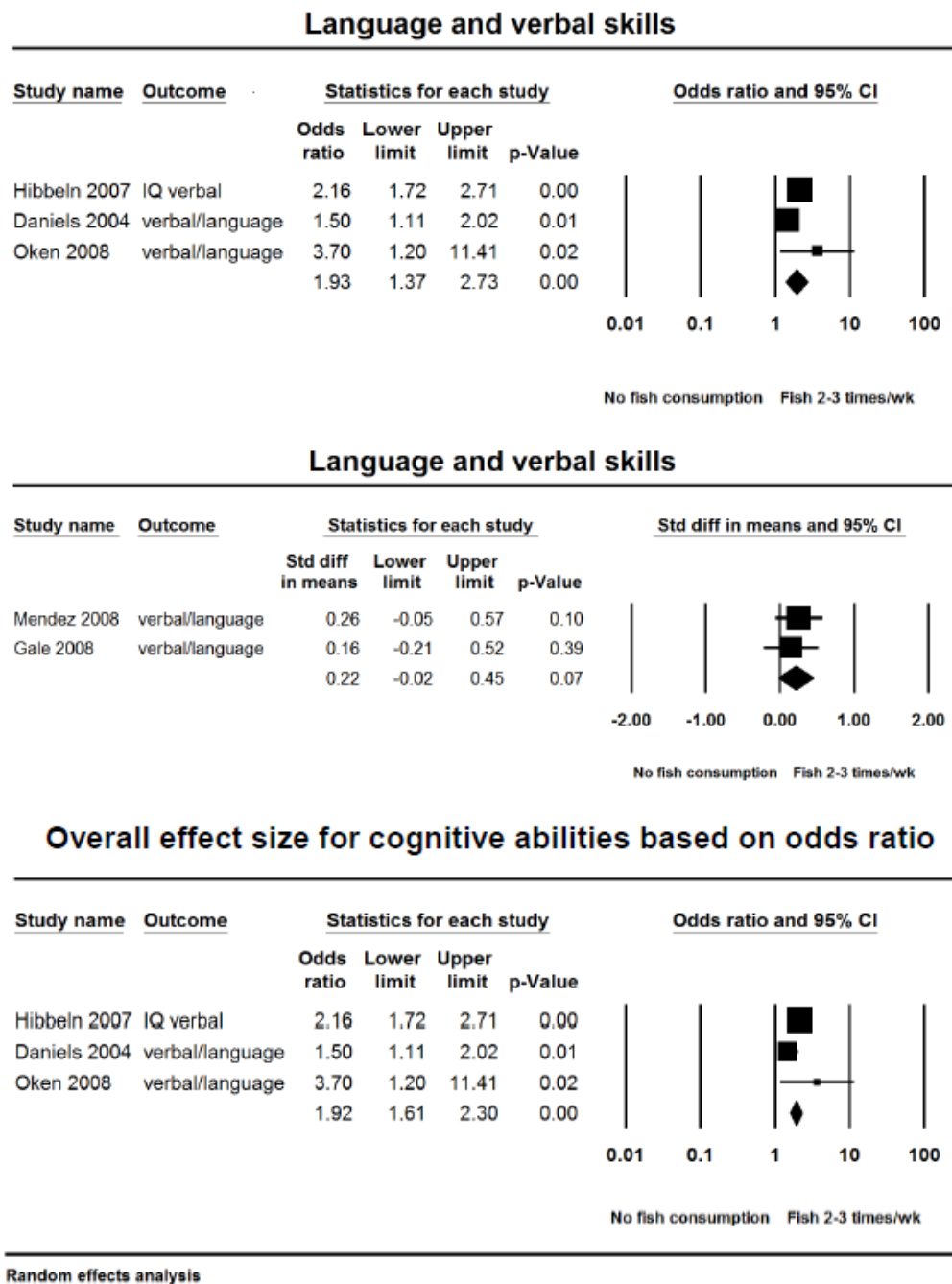


Overall effect size for cognitive abilities in RCTs



Random effects analysis

Figure 6 Meta-Analysis of prenatal fish intake two to three fish servings per week vs no fish intake and the effects of cognitive abilities of the offspring from five observational studies.



3.3.5 Meta-regression

Meta-regression found no effect for age at assessment or DHA dosage in mg per week on offspring cognitive abilities.

3.3.6 Sensitivity analysis

Judged from the Funnel plot and the corresponding Egger's test there was no evidence for publication bias (Figure 7 for RCTs and Figure 8 for OS).

Figure 7 Funnel plot of standardized difference in means by Fisher's Z from Meta-Analysis of RCTs comparing prenatal fish oil intake and the overall effects on children cognitive outcomes. In the absence of publication bias, as demonstrated in this funnel plot.

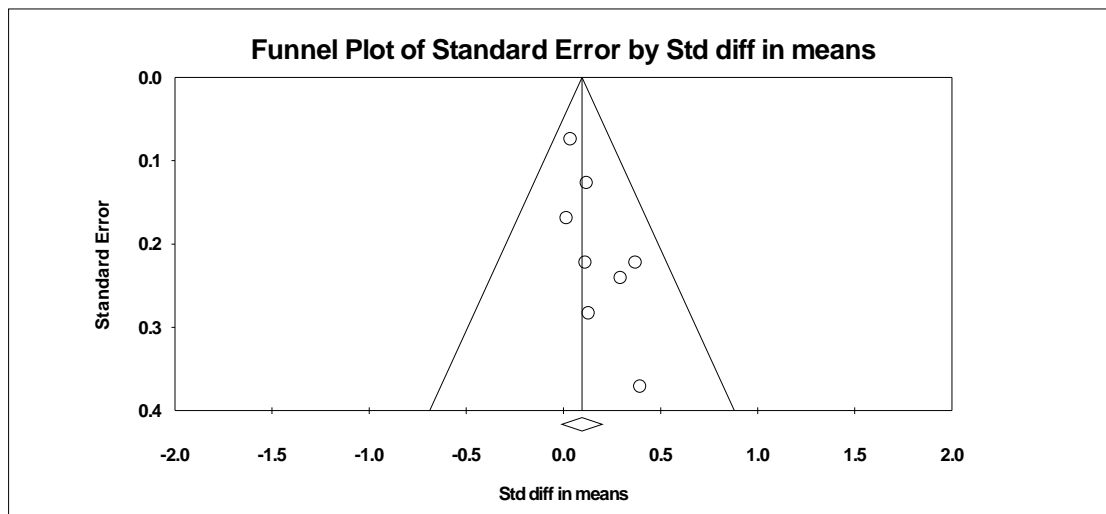


Figure 8 Funnel plot of standard error by Fisher's Z from meta-analyses of observational studies comparing prenatal fish intake (fish consumption 2 to 3 times a week vs no fish consumption) and the effects on children cognitive abilities.

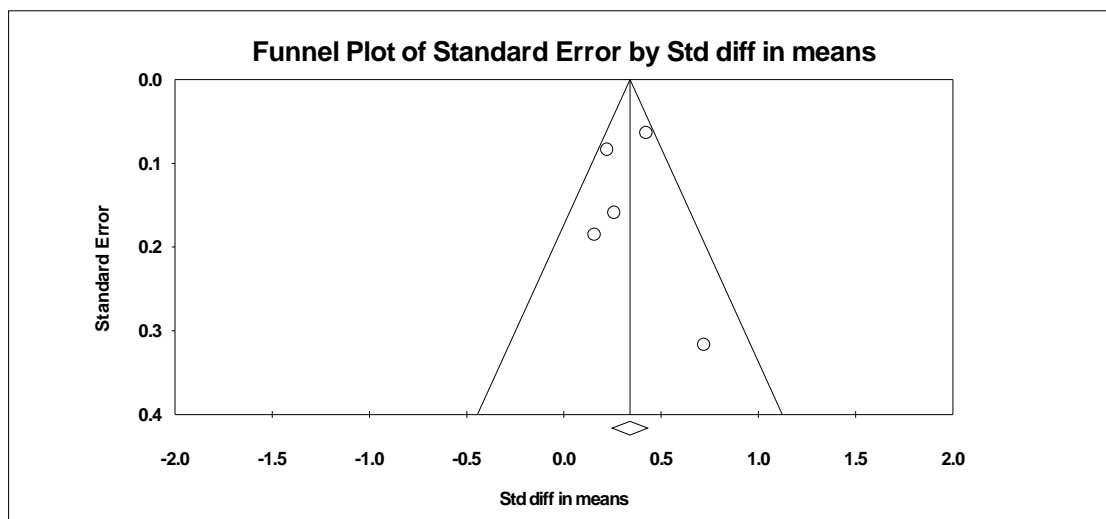
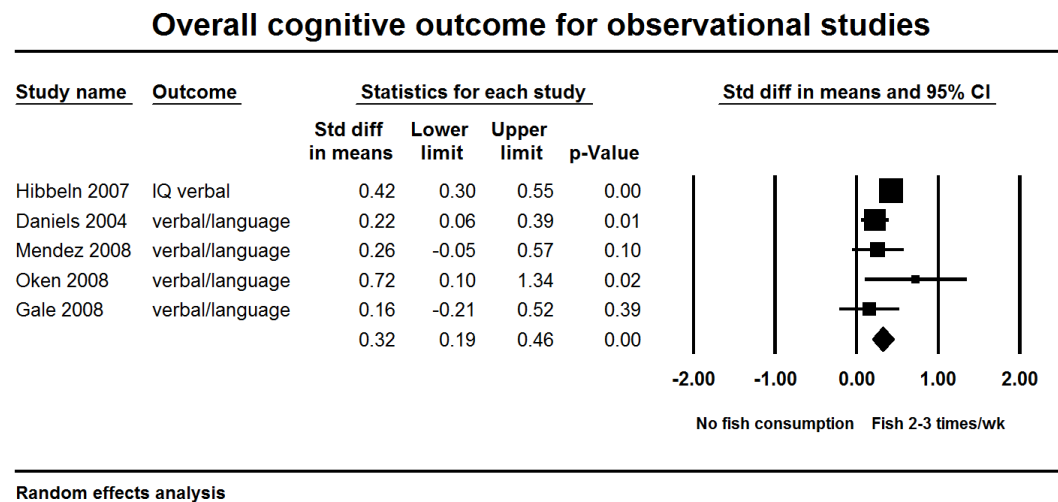


Figure 9 presents the overall summary effect size (observational studies) for maternal fish intake 2 to 3 times a week vs no fish intake and children cognitive abilities for studies reporting the odd ratios and the mean values. The odd ratios were converted into SMD using the method described in the method section (sensitivity analysis section) and were statistically significantly different with pooled SMD of 0.32 [95% CI, 0.19-0.46]; $p < 0.001$).

Figure 9 Meta-Analysis of prenatal fish intake two to three fish servings per week vs no fish intake and the effects of cognitive abilities of the offspring from five observational studies.



Note: We used a basic method suggested by Hasselblad and Hedges (1995) to convert dichotomous outcome into continuous outcomes. The method is based on the assumption that mean scores in each group follow a logistic distribution and that variances are equal between groups:

$$\ln OR = \frac{\pi}{\sqrt{3}} SMD$$

3.4 Discussion

In this comprehensive, up to date review of all available literature, we found that prenatal fish oil was associated with better cognitive abilities in the offspring. Although, the results were not statistically significant, we found concordance across reviewed study designs where RCTs supported the results of the observational studies on this topic.

Evaluations of eight randomized control trials found the results approaching statistical significance towards better cognitive functions among children of mothers in fish oil intervention groups. Examination of specific cognitive outcome showed that fish oil was particularly beneficial for memory functions. Analyses of observational studies suggest that consuming fish 2-3 times a week, which was the most common category of fish consumption by pregnant women in the selected studies, is beneficial for optimal cognitive development of the offspring specifically for domains related to language and verbal skills.

To the best of my knowledge, no previous Meta-Analysis has addressed the problem of presentation of results in a domain-specific way comparing results from epidemiological studies and randomized control trials. A domain-specific presentation of results was incorporated based on the available cognitive domains from published research studies. It should be acknowledged that there is currently only limited information on which specific cognitive abilities are omega-3 sensitive, and there are no common standardized sets of cognitive tests used in nutritional studies. The present finding on better memory and language abilities in children whose mothers consume fish oil in pregnancy could be a potential direction for future studies on this topic.

Starting with the RCTs included in the present study, a number of factors could contribute to the small effects. There was inconsistent dosage across selected studies. The studies included in this Meta-Analysis used various dosages (between 214mg/day to max. 2200mg/day). Currently, the recommended DHA minimum dosage for pregnant women is 300mg per week. One of the RCT included in this Meta-Analysis used the intervention dosage below the minimum recommendation (214mg/d).(Judge et al., 2007) Therefore this could have an impact on the magnitude of the effects from the present analysis. We performed meta-regression of DHA dosage in RCTs but did not find statistically significant results. Visual assessment of the results suggested that higher dosage could be more beneficial.

Another potential factor contributing to small effect sizes could be the cognitive assessment chosen. Inconsistent results may be due to the use of different measures of cognitive functions in

the current literature. Measurement methods must be homogeneous, sensitive, and specific for the different areas of neurodevelopment and this should be considered in future studies on the topic. Also it should be noted that one of the studies used the Fagan Test of Infant Intelligence (Judge et al., 2007). It should be kept in mind that the Fagan test has been developed for the early detection of later mental retardation and should not be used for routine screening with normal populations. In clinical use, the Fagan test should only be given to infants suspected to be at risk for later cognitive deficit (this could account for an incorrect use of the test battery in the study by Judge et al 2007).

The present study examined specific cognitive domains (not only overall cognitive function) and we found language and memory functions to be sensitive to prenatal intake of DHA in children. Future studies should carefully select cognitive measures to assess language and memory cognitive domains. General and specific cognitive domains should be evaluated.

A recent Meta-Analysis (Gould et al., 2013) compared the effect of fish oil on child language development and reported that language development showed no differences between the intervention and placebo groups which is contradictory to the results of the present study. Daniels et al reported that higher maternal fish consumption was associated with better language skills in 7421 British children assessed at 15 months. (Daniels et al., 2004) Oken et al reported that although higher fish intake may result in higher erythrocyte mercury concentration, research in American schoolchildren demonstrated that higher maternal fish intake was positively associated with improved language scores on the Peabody Picture Vocabulary Test (PPVT), after adjustment for multiple potential confounding covariates. (Oken & Bellinger, 2008)

Another factor that could affect the magnitude of the effect sizes was different age at assessments: seven of the twelve studies assessed the neurodevelopment of children at or after 3 years of age and these studies showed no benefit of n-3 LCPUFA supplementation up until 7 years of age. For example, Helland et al reported positive effect of DHA on intellectual abilities of children. (Helland et al., 2003) The present Meta-Analysis performed a meta-regression of the effect of 'age at assessment' on cognitive abilities and found no statistically significant moderating effect.

These results, like those of any Meta-Analysis, should be viewed with caution. Meta-regression is a form of observational association and therefore cannot be used to make causal inferences about the data (Higgins & Thompson, 2004) however in the present study I found no effect for age at assessment or DHA dosage in mg per week on offspring cognitive abilities.

The overall consistency of our findings, regardless of study type, is reassuring. The only major source of bias identified in RCTs was that only four studies reported data for completers.

Assessment of dietary intake of fish, by food frequency questionnaires in observational studies, can be associated with a considerable degree of measurement error even when using validated methods. This is probably one explanation why a dose-response effect could not be shown between change in dietary intake and magnitude of cognitive scores change.

As confirmed above, the more consistent results were obtained in observational studies and can be explained by the possibility that fish, as a whole food, contains other nutrients important to cognitive development (A Nyaradi et al., 2013). However, the long-term effects of fish oil on children's cognitive abilities remain unknown. More research is needed to identify the importance of prenatal intake of omega-3 and the effects on children cognitive abilities.

3.4.1 Conclusion

Intake of fish oil (supplementation or consumption of fatty fish) by pregnant women is positively associated with cognitive abilities in their offspring. Specifically, fish oil is associated with advancement in language and memory abilities.

Chapter 4 Sun Exposure, Vitamin D and Psychotic Experiences

4.1 Summary

Sun exposure is considered the single most important source of vitamin D. Vitamin D deficiency has been suggested to play a role in the aetiology of psychotic disorders. The aim of the present study was to evaluate the association between sun exposure and psychotic experiences in a general population sample of Swedish women. The study population included participants from The Swedish Women's Lifestyle and Health cohort study. The 20-item Community Assessment of Psychic Experiences (CAPE) was administered between ages 30 and 50 to establish psychotic experiences. Sun exposure as measured by 1) sunbathing holidays and 2) history of sunburn was measured between ages 10 to 39. The association between sun exposure and psychotic experiences was evaluated by quantile regression models. 34 279 women were included in the analysis. Women who reported no sunbathing holidays and two or more weeks of sunbathing holidays scored higher on the CAPE scale than women exposed to one week of sunbathing holidays across the entire distribution, when adjusting for age and education. Similarly, compared with women who reported a history of one sunburn, the women with none or two or more sunburns showed higher scores on the CAPE scale with more women in the right part of the distribution. The findings of this study suggest that in a population based cohort of middle aged women, both low and high sun exposure is associated with increased level of positive psychotic experiences.

4.2 Introduction

Schizophrenia and other psychotic disorders are lifelong neuropsychiatric conditions that affect 2- 3% of the population (J. J. McGrath et al., 2015; Perälä et al., 2007). The characteristics of psychosis are altered perception (hallucinations) and changes in the form and content of thoughts and speech (delusions and thought disorder). Symptoms typically begin in late adolescence or early adulthood. Schizophrenia has frequently been associated with abnormalities in the dopaminergic system (Jim van Os & Kapur, 2009).

Vitamin D is an essential nutrient that plays an important role in many biochemical functions that contribute to ageing, including bone renewal, cell proliferation, hormone balance, and cardiovascular and glucose metabolism (Berridge, 2015). Of particular interest is accumulating evidence for the actions of vitamin D in the brain (D. Eyles et al., 2003; Holick & Chen, 2008).

Animal studies have demonstrated that prenatal vitamin D deficiency is associated with persistent changes in adult brain structure, neurochemistry, and behaviour (Burne et al., 2004; D. Eyles et al., 2003). Evidence now links low vitamin D levels with reduced cognitive performance (Annweiler et al., 2010), increased risk for cancer, diabetes, cardiovascular disease, and death (LeBlanc, Chou, Zakher, Daeges, & Pappas, 2014; Pludowski et al., 2013)

The main source of vitamin D for humans is from its dermal synthesis by exposure to sunlight (Lips et al., 2014; Touvier et al., 2015) which provides up to 90% in the form of vitamin D³ (cholecalciferol) with the remainder coming from food in the form of vitamin D³ or vitamin D² (ergocalciferol) (Holick, 2004; Holick & Chen, 2008; LeBlanc et al., 2014; Umhau et al., 2013).

Solar ultraviolet B radiation with a wavelength between 290 and 315 nm, penetrates the skin and converts 7-dehydrocholesterol to pre-vitamin D³, which then is isomerized by heat to vitamin D³ before being carried, bound to vitamin D binding protein, to the liver where it is converted into the main metabolite 25-hydroxyvitamin D₃. Prolonged sun exposure does not result in the production of excess quantities of vitamin D₃ to cause intoxication. Moreover, it has been argued that prolonged exposure can break down vitamin D, reducing health benefits and increasing risk of skin cancer (Holick, 2004). Therefore, it has been suggested that moderate sun exposure is as effective as long sun exposure for previtamin D production (Sivamani et al., 2009). It has been proposed that the increase in serum 25(OH)D attained from exposure to UVB radiation is often more effective than consumption of 1000 IU vitamin D₂ or vitamin D₃ daily (Buettner & Raasch, 1998).

Murri et al reported in a Meta-Analysis that individuals with psychosis showed statistically significantly lower vitamin D levels than healthy controls (Belvederi Murri et al., 2013). Vitamin D has been found to modulate dopamine neurotransmission (D. Eyles et al., 2003) and several studies reported an association between early life vitamin D deficiency and later psychotic disorder. Vitamin D deficiency around birth has been associated with increased risk for later schizophrenia in a Danish population-based study (J. J. McGrath, Eyles, et al., 2010). McGrath and colleagues reported that both low and high concentrations of neonatal vitamin D were associated with increased risk of schizophrenia. Similarly, lack of vitamin D supplementation during the first year of life was found to be associated with later schizophrenia (J. McGrath et al., 2004). However, other studies have failed to find a statistically significant association (Norelli, Coates, & Kovasznay, 2010; Schneider et al., 2000). While there are many studies reporting the association between vitamin D levels in the blood samples (J. McGrath et al., 2004; J. J. McGrath,

Eyles, et al., 2010), there is still a lack of studies on sun exposure, the main source of vitamin D in most countries. Only one study has reported on the relationship between sunlight exposure and schizophrenia incidence, but found no association. This study was limited in power and did not measure sun exposure at the individual level but instead used average sun exposure for a larger geographic area as their exposure (Kendell, 2002). Thus, the association between vitamin D, sun exposure and psychosis remains debated.

Evidence suggests that subclinical psychotic experiences might be on a continuum with psychotic disorders. Psychotic experiences are present in 5-15% of individuals from the general population (J. J. McGrath et al., 2015; J van Os et al., 2009) and share risk factors with psychotic disorders, including social adversity (e.g., low SES, urbanicity) (J van Os et al., 2009) and cognitive impairment (Simons, Jacobs, Jolles, van Os, & Krabbendam, 2007). Imaging studies have also revealed pathophysiological overlaps between psychotic disorders and subclinical psychosis. Moreover, the occurrence of psychotic experiences in early life is associated with increased risk of later psychotic disorders. Psychotic experiences have also been associated with a wider range of common mental health problems, including anxiety, depression, substance misuse, suicide risk and self-harm (Olfson et al., 2002; Rössler et al., 2011; Saha et al., 2011; Saha, Chant, Welham, & McGrath, 2005; J van Os et al., 2009)

Because psychotic experiences are common and associated with a range of adverse health outcomes (J. J. McGrath et al., 2015; J van Os et al., 2009) it is important to study them. Moreover, since individuals with psychotic experiences generally do not receive anti-psychotic medications potential confounding by medication is avoided.

Given the limited research, the aim of this study is to investigate the association between adult life sun exposure (as a proxy for vitamin D status) and later psychotic experiences. Using a large, prospective, population based, cohort study, we tested the hypothesis that sun exposure behaviours predict later psychotic experiences.

4.3 Methods

4.3.1 Study Population

4.3.1.1 Who is the cohort?

The purpose of the Woman Lifestyle and Health (WLH) study was to create a large prospective cohort designed specifically to investigate the association between lifestyle factors (including

dietary habits) and cancer and cardiovascular disease in young women. Other outcomes have also been investigated, including overall mortality and psychiatric conditions.

The WLH study was co-funded by the Swedish Medical Products Agency, the Swedish Cancer Society and three pharmaceutical companies. The ongoing analyses and the follow-up questionnaire were funded by the Swedish Cancer Society and the Swedish Research Council.

Between 1991 and 1992, women were invited to participate in the WLH study. Inclusion criteria were age between 29 and 49 years (born between 1943 and 1962) and residence in the Uppsala Health Care Region, which comprises approximately one-sixth of the Swedish population. Altogether, 96 000 women were randomly selected from the Swedish Population Registry at Statistics Sweden based on their unique, 10-digit national registration number, which includes information on both date of birth and sex. The responsible data monitoring board and the ethical committee in Sweden approved the study design, and all women gave informed consent to participate in the study. The women were mailed an invitation to the study, along with the baseline questionnaire, which included a food frequency questionnaire. In total, 49 259 women (51%) completed and returned the baseline questionnaire, and were thus included in the final cohort.

The median age at enrolment was 40 years, meaning that most women were premenopausal at the time of enrolment. The cohort is generally well-educated, with 68% having completed more than 10 years of schooling, and they also led a generally healthy lifestyle. The median BMI at baseline was 23, only 21% were smokers and only 4% fell into the lowest category of physical activity. Alcohol intake in the cohort was also quite low at baseline, with a median intake of 2.27 g/day. Finally, 13% of the women used oral contraceptives.

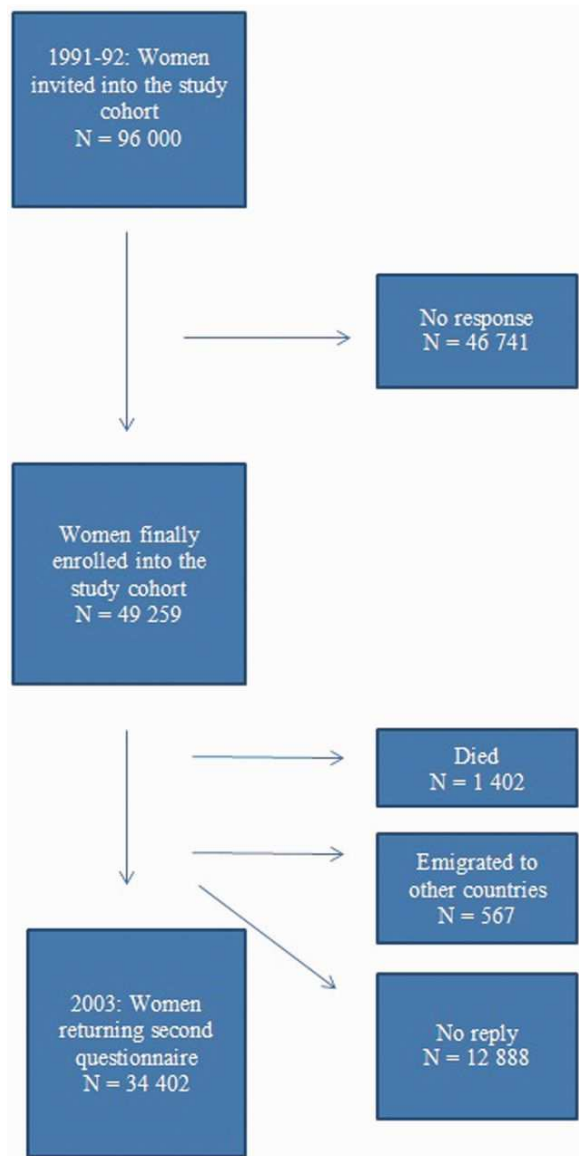
Table 3 Baseline characteristics of participants in the Women's Lifestyle and Health cohort, entire cohort and according to follow-up status. Median and 10–90 percentiles, unless otherwise stated (Roswall et al., 2015)

	Baseline cohort <i>N</i> = 49 259	Responders to the follow-up questionnaire <i>N</i> = 34 402	Non-responders to the follow-up questionnaire <i>N</i> = 14 857
Age at enrolment, years	40 (32–48)	40 (32–48)	40 (32–48)
BMI, kg/m ²	23 (20–28)	22.5 (20–28)	23 (20–28.5)
Missing, <i>N</i> (%)	2024 (4.11%)	1213 (3.53%)	811 (5.46%)
Smoking status, <i>N</i> (%)			
Never	20 476 (41.57%)	14 682 (42.68%)	5794 (39.00%)
Former	18 287 (37.12%)	12 821 (37.27%)	5466 (36.79%)
Current	10 496 (21.31%)	6899 (20.05%)	3597 (24.21%)
Education, <i>N</i> (%)			
0–10 years	14 491 (30.08%)	9160 (27.16%)	5331 (35.88%)
11–13 years	18 797 (39.02%)	13 334 (39.53%)	5463 (36.77%)
>13 years	14 880 (30.89%)	11 236 (33.31%)	3644 (24.53%)
Missing	1091 (2.21%)	672 (1.95%)	419 (2.82%)
Postmenopausal status, <i>N</i> (%)			
Premenopausal	43 112 (87.52%)	30 372 (88.29%)	12 740 (85.75%)
Postmenopausal	4612 (9.37%)	3091 (8.98%)	1523 (10.25%)
Missing	1533 (3.11%)	939 (2.73%)	594 (4.00%)
Oral contraceptive use, <i>N</i> (%)			
Never	8089 (16.42%)	5439 (15.81%)	2650 (17.84%)
Former	34 529 (70.10%)	24 355 (70.80%)	10 174 (68.48%)
Current	6246 (12.68%)	4402 (12.80%)	1844 (12.41%)
Missing	395 (0.80%)	206 (0.60%)	189 (1.27%)
Parity, <i>N</i> children	2 (0–3)	2 (0–3)	2 (0–3)
Missing, <i>N</i> (%)	7044 (14.30%)	4676 (13.59%)	2368 (15.94%)
Physical activity, <i>N</i> (%)			
1 (very low)	2079 (4.22%)	1250 (3.63%)	829 (5.58%)
2 (low)	4992 (10.13%)	3544 (10.30%)	1448 (9.75%)
3 (moderate)	28 007 (56.86%)	19 320 (56.16%)	8687 (58.47%)
4 (high)	7895 (16.03%)	5874 (17.07%)	2021 (13.60%)
5 (very high)	3950 (8.02%)	2940 (8.55%)	1010 (6.8%)
Missing	2336 (4.74%)	1474 (4.28%)	862 (5.80%)
Total energy intake, KJ/day	6371.649 (4108.83–9156.69)	6420.867 (4211.52–9159.79)	6245.77 (3863.3–9147.12)
Missing, <i>N</i> (%)	125 (0.25%)	49 (0.14%)	76 (0.51%)
Alcohol intake, g/day	2.27 (0–8.38)	2.41 (0–8.48)	1.97 (0–8.07)
Missing, <i>N</i> (%)	6348 (12.89%)	4043 (11.75%)	2305 (15.51%)

4.3.1.2 Follow up

In 2002/2003 a follow-up study was initiated and women, who had responded to the 1991/1992 questionnaire, were alive, and living in Sweden in October 2002 were contacted. Since 1991/1992, 1,402 women were deceased, and 567 women had emigrated. 47,859 women were invited to participate. 34,415 women (73%) returned the questionnaire which included psychotic experiences using the CAPE scale. The study group which consisted of 73% of the whole cohort was similar to the latter with respect to age, and education, the main confounders included in the analysis (table 3).

Figure 10 Flowchart of participants invited and included in the WLH-study.



4.3.2 Measures

4.3.2.1 Psychotic Experiences

The Community Assessment of Psychic Experiences (CAPE) (<http://www.cape42.homestead.com>) was used to measure psychotic experiences. This is a modified version of the Peters et al. Delusions Inventory, which is based on the 9th edition of the Present State Examination (Peters, Joseph, & Garety, 1999). Our version of the CAPE questionnaire contained 20 questions on psychotic-like symptoms, including only the positive symptoms. The full 42-item CAPE has three subscales (positive, depressive and negative symptoms) and demonstrates satisfactory reliability, construct and discriminant validity (Brenner et al., 2007; Fonseca-Pedrero, Paino, Lemos-Giráldez, & Muñiz, 2012). The 20-item positive scale most strongly predicts future psychosis (Welham et al., 2009). The CAPE is a stable, valid and reliable self-report instrument for the measurement of psychotic-like experiences in the general population based on cross-validation with interview-based data (Konings, Bak, Hanssen, van Os, & Krabbendam, 2006). The degree of distress associated with the experience was not included in the current study. The questions were translated from English into Swedish and back-translated to increase fidelity to the original scale.

Many epidemiological studies chose to group or categorise data. As a main outcome variable in this study, for more efficient use of the true CAPE scale, we calculated the mean CAPE score across all 20 items where, only women with non-missing data were included.

Table 4 Questions on positive psychotic-like symptoms only (Community Assessment of Psychic Experiences, CAPE-42), included in the follow-up study of Women's Lifestyle and Health Cohort.

Questions		Answer alternatives			
		Almost always	Often	Sometimes	Never
1.	Do you ever feel as if people seem to drop hints about you or say things with a double meaning?				
2.	Do you ever feel as if things written in magazines or on TV are especially for you?				
3.	Do you ever feel as if some people are not what they seem to be?				
4.	Do you ever feel as if you are being persecuted in some way?				
5.	Do you ever feel as if there is a conspiracy against you?				
6.	Do you ever feel as if you are destined to be someone very important?				
7.	Do you ever feel that you are a very special or unusual person?				
8.	Do you ever think that people can communicate telepathically?				
9.	Do you ever feel as if electrical devices such as computers can influence the way you think?				
10.	Do you believe in the power of witchcraft, voodoo or the occult?				
11.	Do you ever feel that people look at you oddly because of your appearance?				
12.	Do you ever feel as if the thoughts in your head are being taken away from you?				
13.	Do you ever feel as if the thoughts in your head are not your own?				
14.	Have your thoughts ever been so vivid that you were worried other people would hear them?				
15.	Do you ever hear your own thoughts being echoed back to you?				
16.	Do you ever feel as if you are under the control of some force or power other than yourself?				
17.	Do you ever hear voices when you are alone?				

18.	Do you ever hear voices talking to each other when you are alone?				
19.	Do you ever feel as if a double has taken the place of a family member, friend, or acquaintance?				
20.	Do you ever see objects, people or animals that other people cannot see?				

4.3.2.2 Sun Exposure

Sun exposure was measured at baseline by the following two variables:

HISTORY OF SUNBURN: For each 10 year age period (10–19, 20–29 and 30-39), the participants were asked to report the number of times per year they had been burned by the sun (in Sweden or on beach holiday abroad) so severely that it resulted in pain or blisters that subsequently peeled by choosing from among five categories: never, one time per year, two or three times per year, four or five times per year, or six or more times per year.

SUNBATHING HOLIDAYS: Participants reported the average number of weeks per year spent on sunbathing vacations in Sweden or in southern latitudes (at this time typically southern Europe, e.g., Spain or Greece) for each age decade by choosing from among five categories: never, 1 week per year, 2–3 weeks per year, 4–6 weeks per year, or ≥ 7 weeks per year.

For each category of sun exposure history, we combined exposure across the three decades: 10–19 years, 20–29 years and 30-39 years. Thus, we created three categories for each sun exposure variable: Sunbathing holidays (Never; 1 week per year; ≥ 2 weeks per year) and History of sunburn (None; 1 time; ≥ 2 times).

4.3.3 Confounders

Lifestyle factors controlling access to sunbathing vacation and awareness of sun-protection as well as psychosis risk can be assumed depending on socio-economic status (SES) and age. For this reason we considered years spent in education and attained age (in years) as possible confounders in all our analyses.

SES can be measured as univariate measure of educational attainment. It has been suggested that for those older than 25 years, which is the case in our cohort, educational attainment is an

excellent proxy measure of SES. One reason for this is that after age 25, educational attainment is relatively constant (those pursuing advanced degrees after age 25 are typically high achievers). Another reason is that educational attainment is relatively easy to measure and, unlike income, respondents are often willing to answer questions honestly. For the purpose of this thesis and based on available data, we measured educational attainment by years spent in education.

4.3.4 Statistical analysis

We calculated summary statistics to compare women with different levels of sun-exposure. We summarized the CAPE scale by plotting side-by-side bar segmented bar charts. We included one bar for each of the 20 items of the CAPE scale. Each bar is further sub-divided in segments, one segment for each level of the item, where the size of each segment in the figure is proportional to the number of women with this response. The SAS program for this bar chart is presented below.

4.3.4.1 Quantile regression

To test and estimate the association between different levels of sun-exposure (high and none vs intermediate exposure) and change in the CAPE scale we fitted quantile regression (Cade & Noon, 2003). Whereas a t-test or a linear regression can test for a change in the mean between different groups of exposure, quantile regression allows a comparison of the entire distribution, not only the mean. Similar to estimating a change in mean CAPE we estimated the change in median CAPE. More specifically, we estimated change in the 10th, 20th ... 90th CAPE percentile. (As a comment, 10 percent of the data will be found below the 10th percentile, 20 percent below the 20th percentile etc. and the 50th percentile is usually referred to as the median). We plotted the difference between exposure groups at each 10th CAPE percentile allowing a visual comparison between women subject to different levels of sun-exposure. We fitted quantile regression for each of the two sun-exposure covariates, sunbathing holidays and history of sunburns, separately. All models also included the potential confounders, years in education and age at cohort entry.

In a quantile regression model, in the simplest situation, the outcome needs to be a continuous variable, but both categorical and continuous predictors can be included. As explained in the methods section of this chapter, the outcome measure namely CAPE scores were converted to a continuous variable. Thus, there are several advantages to using quantile regression when comparing two exposure groups. First, using quantile regression allows us to compare the entire

CAPE distribution not only the mean. We hypothesized that a change in sun-exposure would primarily be seen in the right most tail of the CAPE distribution where the women with most psychotic experiences are to be found. Second, quantile regression is a technique robust against single gross outliers and do not rely on assumptions of the data following a particular distribution such as the Gaussian or the binomial.

For both sun exposure variables the intermediate and most common sun exposure (1 week or 1 time) were chosen as the reference category. For each sun-exposure variable and each 10th percentile comparing two levels of sun-exposure (high vs intermediate and none vs intermediate) we calculated the difference in 10th percentiles together with the two-sided 95% confidence intervals using bootstrap(He & Hu, 2002). The SAS program for my main analysis and data set development is presented in Appendix section.

We also performed a set of sensitivity analyses. First, we explored the exposure in different ages of life by refitting the models described above, but for sun-exposure during ages 10 to 19 (adolescence period) and ages 20 to 29 separately (adulthood period). Second, of the 49,259 women in the cohort 1991/92, 34,402 (70%) women returned for the follow-up in 2004 when PE was measured. Missing values and dropouts due to a mechanism acting as a confounder between sun exposure and PE and a not missing at random (MAR) could potentially bias the results(Little & Rubin, 1987). We did not find any logical reason why this should be the case. Still, in a sensitivity analysis we addressed this potential problem by first comparing the covariate distribution among the women entering the cohort 1991 with the women returning for the follow-up. Inverse probability weighting (IPW) is one of several methods that can reduce this bias(Seaman & White, 2011). In this method, complete cases are weighted by the inverse of their probability of being a complete case. We applied this method.

Statistical analyses were performed using the SAS version 9.4.

4.4 Results

The population consisted of N= 34,297 women who reported data on the CAPE questionnaire in 2004. There were women with missing values on sun-exposure N=1,252 and N=663 women with missing values on the confounder (years in education). When filling in the questionnaire the women were between 30 and 50 years old (mean=40.4, Standard Deviation =5.7). The average

number of years in education was 12.4 years (Minimum=0, Maximum=40; Standard Deviation =3.0) (Table 5).

Table 5 Cohort characteristics by levels of sun exposure at ages 10-39.

	Cohort	Age at assessment M(SD)	Education* M(SD)
Sun exposure	<i>N</i>		
Annual cumulative number of weeks spent on sunbathing holidays:	33,745		
<i>Never</i>	3913	41.7(5.7)	11.7(3.3)
<i>1 week per year</i>	10,126	40.5(5.6)	12.4(3.0)
<i>≥2 weeks per year</i>	19,706	40 (5.7)	12.6(2.9)
History of sunburns:	33,597		
<i>None</i>	2683	41.8(5.8)	11.3(2.9)
<i>1 time</i>	18,722	40.7(5.7)	12.4(3.0)
<i>≥2 times</i>	12,192	39.5(5.7)	12.7(2.9)

Note 5 All values reported as mean (SD).

*Average years spent in education

The distribution of the 20 items defining the psychotic experiences is presented in Figure 11. The mean response scores for each item of the CAPE scale is presented in Table 6. In the entire

population, the distribution of CAPE scores was mildly skewed; the mean (SD) for all subjects was 1.19 (0.19). In an ideal population entirely free of psychotic symptoms each of the 20 items in the CAPE scale should have the weight 1:20. Items related to 'Messages from TV', 'Witchcraft, voodoo or the occult' and 'Odd appearance' had average of 1.1 to 1.3; 'Being important', 'Being special' and 'Double meaning'- an average of 1.3 and 1.5 while items 'Telepathy' and 'False appearance' had an population average of 1.6 and 1.7 (Figure 11; Table 6).

Figure 11 Response frequencies (%) of CAPE (20 Items) scores amongst 34,297 population based cohort of Swedish middle aged women.

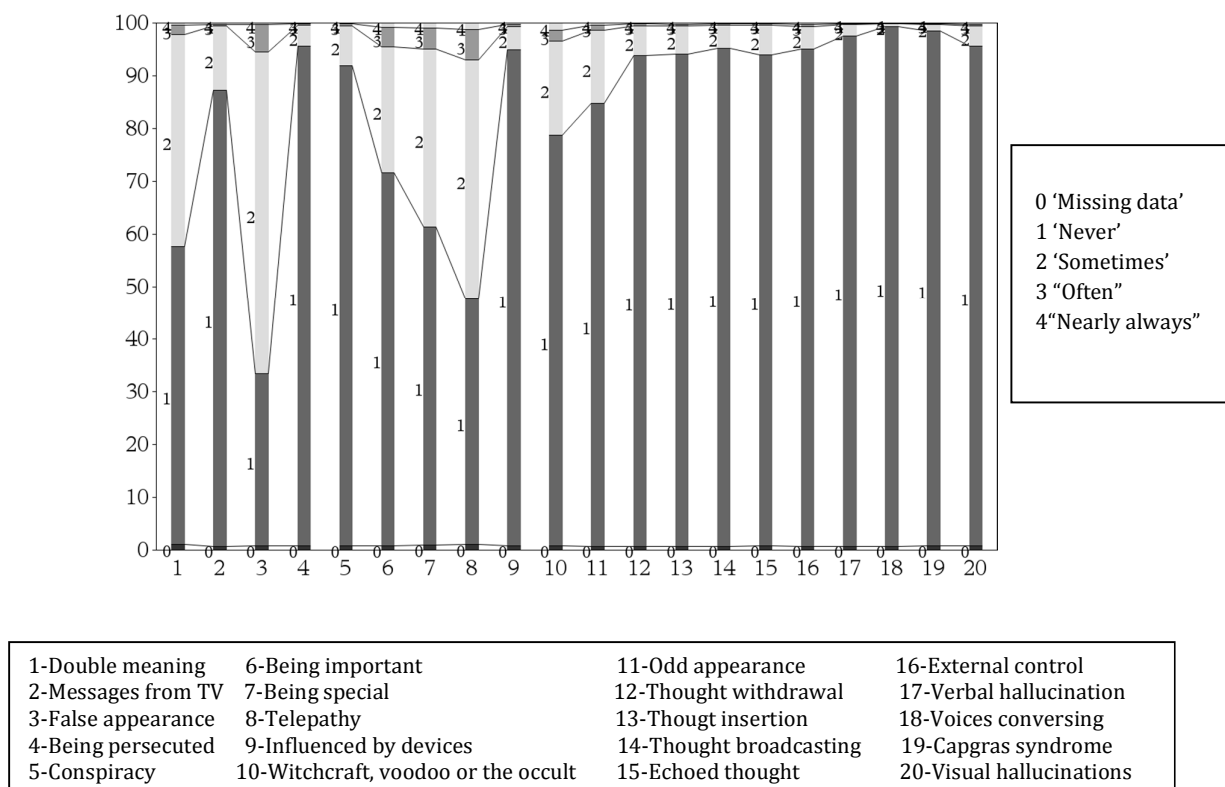


Table 6 Mean values for 20 items of the CAPE scale.

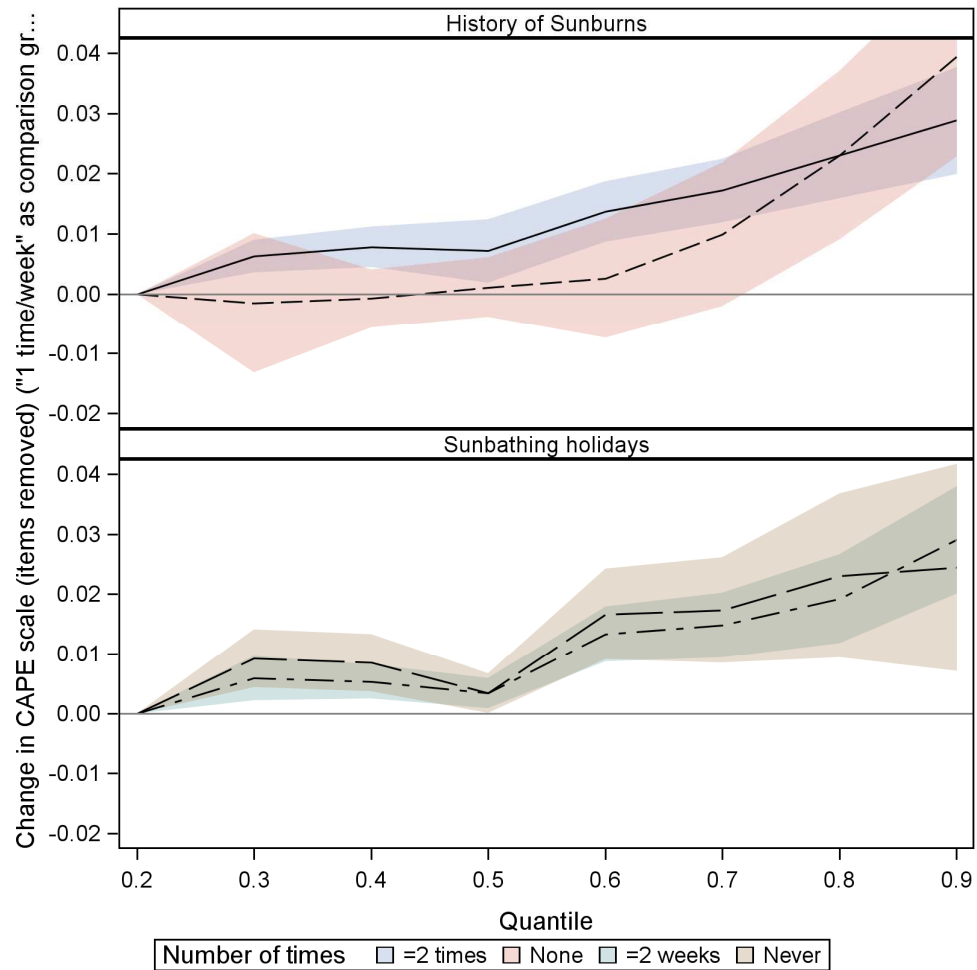
CAPE items	Label	N	Mean	SD
3	False appearance	34118	1.7	0.6
8	Telepathy	34050	1.6	0.7
1	Double meaning	34025	1.5	0.6
7	'Being special'	34111	1.5	0.6
6	Being important	34136	1.3	0.6
10	Witchcraft, voodoo or the occult	34131	1.3	0.6
11	Odd appearance	34182	1.2	0.4
2	Messages from TV	34175	1.1	0.4
4	Being persecuted	34152	1.1	0.3
5	Conspiracy	34137	1.1	0.3
9	Influenced by devices	34147	1.1	0.3
12	Thought withdrawal	34178	1.1	0.3
13	Thought insertion	34183	1.1	0.3
14	Thought broadcasting	34186	1.1	0.3
15	Echoed thought	34153	1.1	0.3
16	External control	34162	1.1	0.3
20	Visual hallucinations	34131	1.1	0.3
17	Verbal hallucinations	34168	1	0.2
18	Voices conversing	34163	1	0.2
19	Capgras syndrome	34154	1	0.2

Note 6 SD= Standard Deviation

Compared with women who reported a history of one sunburn, the women with 'None' or ≥ 2 sunburn showed higher scores on the CAPE scale with more women in the right part of the distribution (Figure 12, Top panel). The psychotic experiences median (50th percentile), 80th percentile and 90th percentile difference for ≥ 2 sunburn vs 1 sunburn was estimated to 0.01 (95%CI: 0.002-0.012), 0.02 (95%CI: 0.016-0.030) and 0.03 (95%CI: 0.019-0.037) respectively. The PEs for women reporting 1 sunburn vs none were higher and statistically significant at 80th and 90th percentile only and was estimated to 0.02 (95%CI: 0.009-0.037), 0.04 (95%CI: 0.022-0.056) respectively. Results for all 10th percentiles are presented in Table 7.

Similarly, compared with women exposed to 1 week of sunbathing holidays, the women with none or ≥ 2 weeks showed higher scores on CAPE scale (Figure 12, Bottom panel). The results were statistically significant across the entire distribution of the CAPE scale. The psychotic experiences median (50th percentile), 80th percentile and 90th percentile difference for ≥ 2 weeks vs 1 week of sunbathing vacation was estimated to 0.003 (95%CI: 0.009-0.006), 0.02 (95%CI: 0.012-0.026) and 0.03 (95%CI: 0.020-0.038) respectively. The psychotic experiences median (50th percentile), 80th and 90th percentile difference for 'Never' vs '1 week' of sunbathing vacation was estimated to 0.03 (95%CI: 0.000-0.006), 0.02 (95%CI: 0.009-0.036) and 0.02 (95%CI: 0.007-0.041) respectively. Results for all 10th percentiles are presented in Table 8.

Figure 12 Distribution of PEs by cumulative sun exposure (history of sunburns at age 10-39 compared to '1 time/week' and sunbathing holidays at age 10-39 compared to holidays '1 week' (adjusted for age, education).



Note 7 Change in CAPE scale ("1 time/week as comparison group)

Table 7 Quantile regression estimates for PLEs by levels of history of sunburns (adjusted for age and education).

Quantile	Categories of history of sunburns ('1 time' as a comparison group)	Estimate	95% Lower Confidence Limit	95% Upper Confidence Limit	P value
0.1	None	0	0	0	0.0006
0.1	≥2 times	0	0	0	0.0008
0.2	None	0	0	0	0.0002
0.2	≥2 times	0	0	0	0.0012
0.3	None	-0.0016	-0.0132	0.0101	0.7923
0.3	≥2 times	0.0063	0.0035	0.009	<.0001
0.4	None	-0.0008	-0.0056	0.0041	0.7522
0.4	≥2 times	0.0078	0.0045	0.0112	<.0001
0.5	None	0.0011	-0.0039	0.006	0.6643
0.5	≥2 times	0.0072	0.0019	0.0124	0.0079
0.6	None	0.0026	-0.0074	0.0125	0.6147
0.6	≥2 times	0.0137	0.0087	0.0187	<.0001
0.7	None	0.0099	-0.002	0.0218	0.1035
0.7	≥2 times	0.0172	0.0119	0.0225	<.0001
0.8	None	0.0231	0.0091	0.0371	0.0012
0.8	≥2 times	0.0231	0.0159	0.0302	<.0001
0.9	None	0.0394	0.0228	0.056	<.0001
0.9	≥2 times	0.0288	0.0199	0.0377	<.0001

Table 8 Quantile regression estimates for PEs by levels of sunbathing holidays (adjusted for age and education).

Quantile	Categories of sun exposure ('1 week' as a comparison group)	Estimate	95% Lower Confidence Limit	95% Upper Confidence Limit	P value
0.1	Never	0	0	0	0.001
0.1	≥2 weeks	0	0	0	0.0035
0.2	Never	0	0	0	0.0012
0.2	≥2 weeks	0	0	0	0.0044
0.3	Never	0.0092	0.0044	0.0141	0.0002
0.3	≥2 weeks	0.0059	0.0021	0.0096	0.002
0.4	Never	0.0085	0.0037	0.0134	0.0006
0.4	≥2 weeks	0.0053	0.0024	0.0082	0.0003
0.5	Never	0.0034	0.0001	0.0067	0.0428
0.5	≥2 weeks	0.0034	0.0009	0.0059	0.0078
0.6	Never	0.0167	0.0091	0.0242	<.0001
0.6	≥2 weeks	0.0133	0.0087	0.018	<.0001
0.7	Never	0.0173	0.0084	0.0261	0.0001
0.7	≥2 weeks	0.0148	0.0094	0.0202	<.0001
0.8	Never	0.0231	0.0094	0.0368	0.001
0.8	≥2 weeks	0.0192	0.0118	0.0267	<.0001
0.9	Never	0.0244	0.0071	0.0417	0.0056
0.9	≥2 weeks	0.0291	0.0202	0.038	<.0001

The results were comparable when restricting the analyses to sun exposure at specific age periods; ages 10-19 and ages 20-39 (Figure 13 and Figure 14).

Figure 13 Distribution of PEs by levels of sun exposure at age 10-19 (history of sunburns at age 10-19 compared to '1 time' and sunbathing holidays at age 10-19 compared to holidays '1 week' (adjusted for age and education).

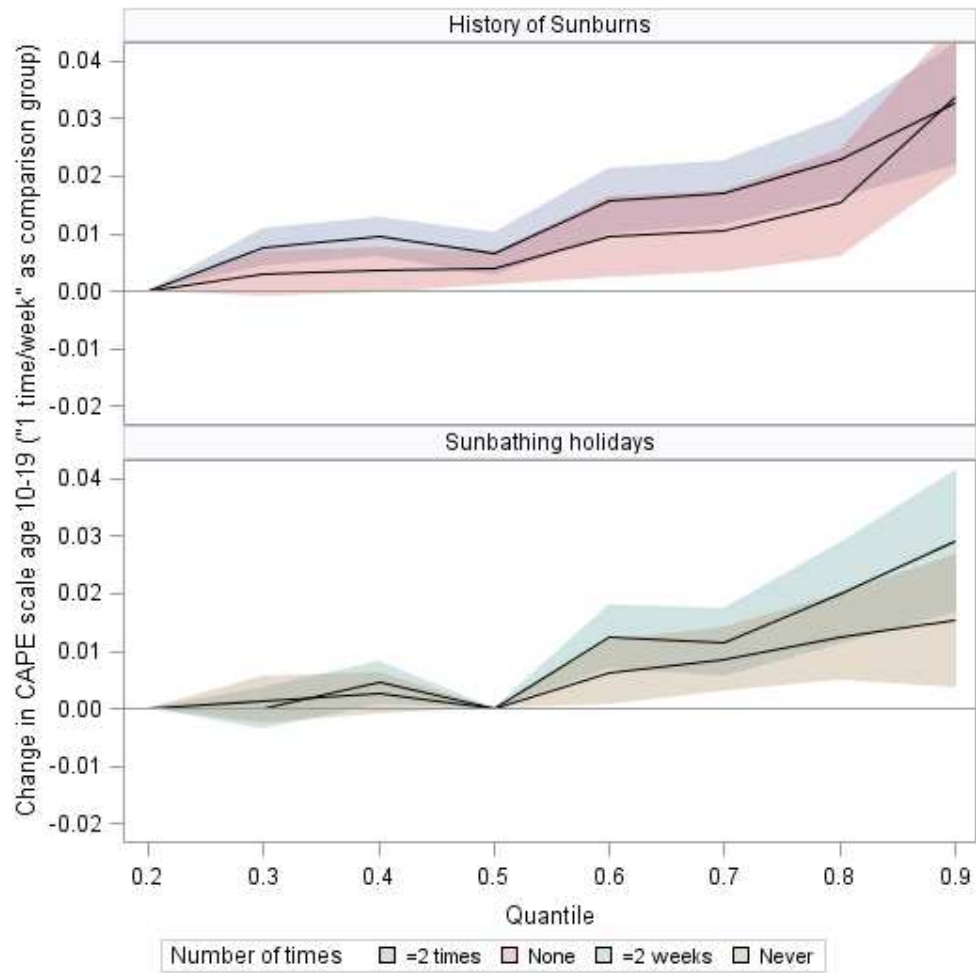
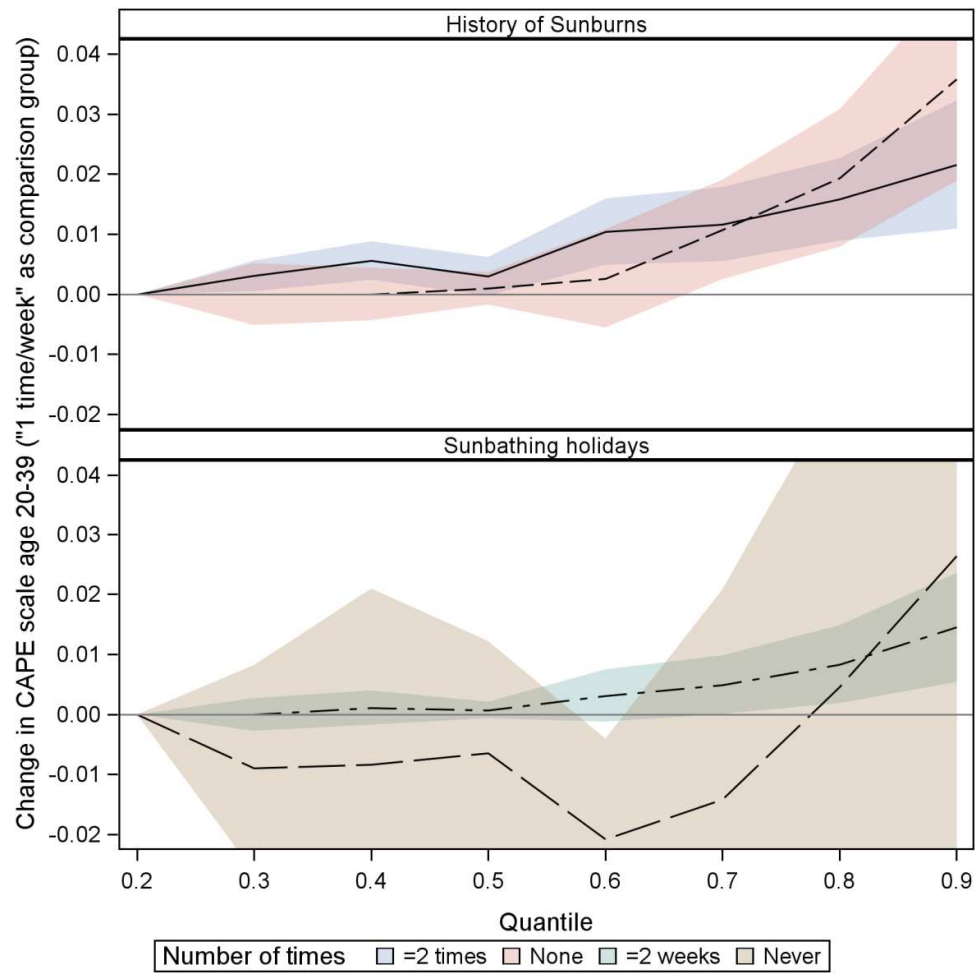
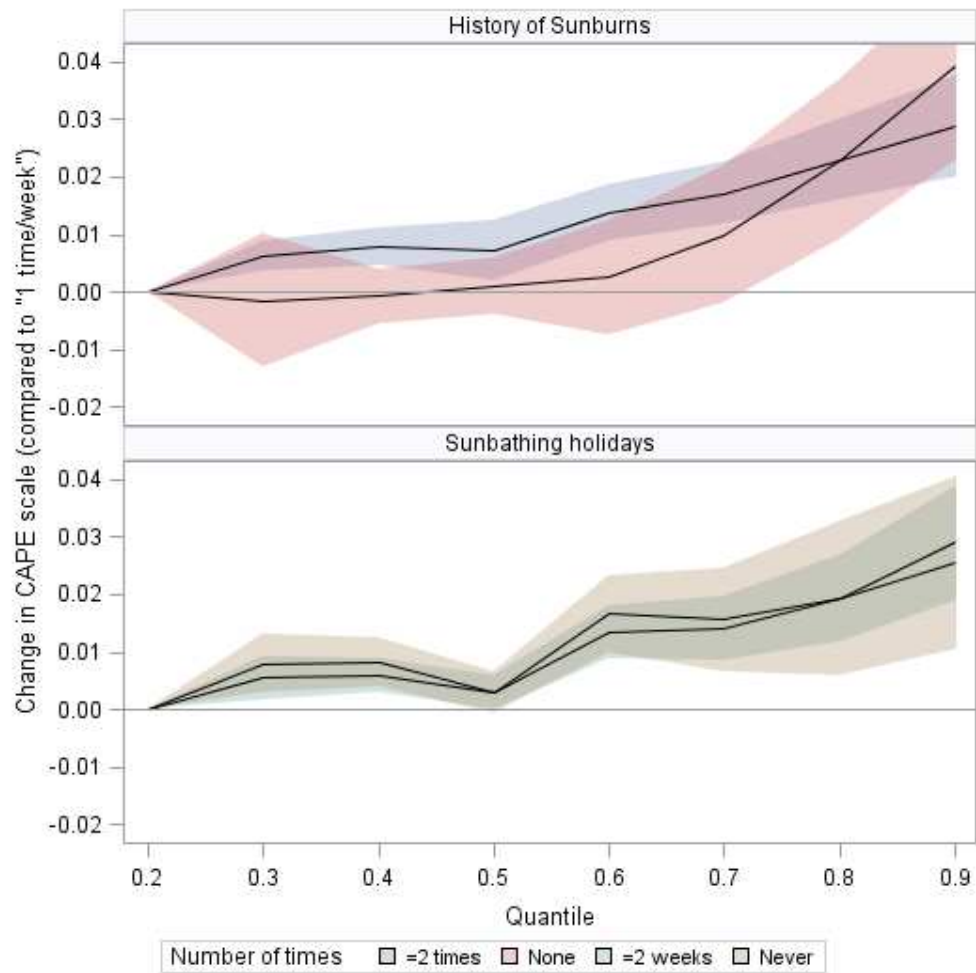


Figure 14 Distribution of PEs by sun exposure at age 20-39 (history of sunburns at age 20-39 compared to '1time' and sunbathing holidays at age 20-39 compared to holidays '1 week' (adjusted for age and education).



I predicted probabilities of participating in the follow up part of the study based on subject characteristics. After applying the weights to the quantile regression models, we concluded that the estimates did not differ from the original estimates (Figure 15).

Figure 15 Distribution of PEs by levels of sun exposure at age 20-39 (history of sunburns at age 20-39 compared to '1 time' and sunbathing holidays at age 20-39 compared to holidays '1 week' (after applying 'Inverse Probability Weighting' method).



4.5 Discussion

In the Nordic countries, as elsewhere, sun exposure is by far the most important source of vitamin D. In a population based cohort of 34,402 women we found an association between cumulative measures of sun exposure at ages 10 to 39 years and positive psychotic experiences. We observed a U-shaped association where women with low sun exposure as well as women with high sun exposure reported more psychotic experiences compared to women with an intermediate level of sun exposure.

The U-shaped association is consistent with previous studies on vitamin D and health outcomes (J. J. McGrath, Eyles, et al., 2010) which reported a 2-fold increased risk of schizophrenia in those in the lower quartile compared to those in the fourth quartile. Additionally, those in the highest quartile of vitamin D levels had a statistically significant increased risk of schizophrenia compared with those in the fourth quintile.

The non-linearity in the association might argue against a possible causal relationship. However, the associations with sun exposure and health outcomes are often non-linear with advantageous effects of a balanced exposure (WHO, n.d.).

An earlier study using the same cohort of women as in this study showed that vitamin D intake from the diet was statistically significantly associated with a decreased relative risk of both medium and high levels of psychotic symptoms (Hedelin et al., 2010). The present study examined the sun exposure variables considering sun exposure as a main source for vitamin D levels and not diet (Holick, 2004; LeBlanc et al., 2014; Umhau et al., 2013). Additionally, in the present study I used the entire CAPE scale instead of categorizing the responses which might exclude important information.

Consequently, a major strength of my study is the detailed assessment of sun exposure during different periods of life. The information on sun exposure habits was gathered at the start of the study which minimizes the risk of reverse causality. This study possibly includes non-differential (or random) measurement as sun exposure information was collected retrospectively. This might attenuate examined associations. Such measurement error could under-estimate the true association.

Another major strength of this study is use of an unselected large population-based cohort drawn from the Swedish National Population Register and followed for over 10 years.

In the present study I performed a quantile regression, an approach particularly suitable for epidemiologists, since scientific interest is often on high or low, e.g.(Hedelin et al., 2010) – rather than average – degrees of response. This approach is particularly important when assessing a risk factor that does not have a linear relationship. From a public health and nutrition policy perspective, specific areas of the outcome distribution are likely to be of more interest than others. For example, instead of focusing on the mean of the dependent variable, scientists could explore characteristics (individual, social, environmental) that are associated with this variable, which are of concern once they are linked to chronic diseases. These associations are subject to exploration even when the mean of the dependent variable is not significantly associated with a set of covariates (Cade & Noon, 2003).

Our study has several limitations. We had no biological data on vitamin D levels, which could have established a clear link to vitamin D and yet it is well known that sun exposure is the most important determinant of vitamin D status (Holick, 2004; LeBlanc et al., 2014). Additionally, the assumption was made that sun exposure habits did not change over time and consequently, information from one assessment alone was used in the models. This is a common assumption in cohort studies and tends to underestimate risk. However, the questionnaire took into consideration changes, as it asked about exposure in different decades.

The current study was based on multiple exposure factors (several sun exposure variables) as proxies for vitamin D level and their relationship with psychotic experiences. The estimates were adjusted for confounding effects and each exposure variable was assessed independently in order to detect any potential effect. Still, our results should be interpreted cautiously. Even well-designed observational studies can be influenced by residual confounding. There may also be a number of unknown factors that we did not take into consideration in our study, which could influence psychotic experiences and be related to sun exposure.

We did not have data on the full CAPE scale, but only the positive symptoms. Moreover, the degree of distress associated with psychotic experiences was not included in the current study, which could have allowed a more detailed analysis on items and dimensions. The CAPE scale of psychotic experiences are correlated with measures of general psychopathology, including depression. The association between the positive and the depressive dimension in CAPE, which we could not include for practical reasons, is fairly low when distress associated with positive symptoms is held constant ($r = 0.25$) (Stefanis et al., 2002). As a consequence, the dimension of positive symptoms are believed to be considered an independent dimension. Further, data on

psychotic experiences were not measured at baseline therefore reverse causality could be a potential explanation of findings.

In terms of generalizability of the present study, males were not included and previous reports suggest a gender difference in the incidence of psychosis. However, in general population samples, psychotic experiences are found to be equally distributed among males and females(Peters et al., 1999)(Varghese, Scott, & McGrath, 2008).

4.5.1 CONCLUSION

Both low and high sun exposure is associated with increased levels of psychotic experiences. Previous studies have reported associations between vitamin D and increased risk for health problems, such as schizophrenia, as well as clinical symptoms in patients with mental health problems. However, there is a lack of previous studies on how sun exposure, the main source of vitamin D, influences psychotic experiences in the general population. This study's contribution to the literature is that in the general population of Swedish women sun exposure has a U-shaped association with positive psychotic experiences.

Chapter 5 Sun Exposure, Vitamin D and Depressive Symptoms

5.1 Summary

UV exposure is the most important source of vitamin D. Vitamin D deficiency has been suggested to play a role in the aetiology of mood disorders. The aim of the present study was to examine the association between sun exposure behaviours and depressive symptoms in a general population sample of Swedish women. The study population included participants from The Swedish Women's Lifestyle and Health cohort study. A questionnaire (based on DSM IV criteria for depression) was administered to study participants between ages 30 and 50 to establish depressive symptoms. Sun exposure as measured by 1) sunbathing holidays and 2) history of sunburn was measured between ages 10 to 39. The association between sun exposure and depressive symptoms was evaluated by logistic regression models. 34 010 women were included in the analysis. Women who reported a history of two or more sunburns showed positive association with depressive symptoms, compared to history of a single sunburn, when adjusting for age and education. The same association was not evident for sunbathing holidays and depressive symptoms. The findings of this study suggest that in a population based cohort of middle aged women, high sun exposure is associated with an occurrence of depressive symptoms.

5.2 Introduction

Mental health problems, including depression, are major contributors to health morbidity and mortality worldwide. Depressive symptoms were previously reported in a general population and one study showed that of the nine symptoms assessed, the most frequently occurring were dysphoric mood, increased sleep, and loss of interest in other people or activities previously enjoyed (Henderson & Pollard, 1992). The findings provide evidence that various symptoms of depression may be more common in the general population than previously suspected (Henderson & Pollard, 1992).

Insufficient sun exposure and vitamin D deficiency have both been associated with increased risk of depression. A UK based prospective study of children (ALSPAC) found higher concentrations of season-adjusted 25(OH)D₃ assessed at mean age 9.8 years to be associated with lower levels

of depressive symptoms at age 13.8 years and with increased odds of decreasing symptoms between age 10.6 and 13.8 years (A.-M. Tolppanen et al., 2012).

In a recent Meta-Analysis vitamin D deficiency has been documented in patients with depression (Anglin et al., 2013). Considering the high prevalence of both vitamin D deficiency and depression, an association between these two conditions would have significant public health implications. The observational studies to date provide some evidence for a relationship (Kerr et al., 2015; Wilkins, Sheline, Roe, Birge, & Morris, 2006), but there is no evidence for an association between vitamin D from sun exposure and depressive symptoms in the general population. Because depressive symptoms are common and associated with a range of adverse health outcomes (Black, Markides, & Ray, 2003; Del Pozo-Cruz et al., 2015; Doğan, Onat, Kaya, Ayhan, & Can, 2011) it is important to study them. Moreover, since individuals with depressive symptoms generally do not receive anti-depressive medications potential confounding by medication is avoided.

The biological mechanism whereby vitamin D might be associated with psychiatric illnesses is not well understood. Vitamin D is an essential nutrient that plays an important role in many biochemical functions that contribute to ageing, including bone renewal, cell proliferation, hormone balance, and cardiovascular and glucose metabolism (Berridge, 2015). Of particular interest is accumulating evidence for the actions of vitamin D in the brain (Cui et al., 2014; D. Eyles et al., 2003; Holick & Chen, 2008). Vitamin D is involved in the synthesis of serotonin and dopamine within the brain, both chemicals linked to depression. Evidence now links low vitamin D levels with reduced cognitive performance (Annweiler et al., 2010; Wilkins et al., 2006), increased risk for cancer, diabetes, cardiovascular disease, and death (Grant et al., 2015; LeBlanc et al., 2014; Pludowski et al., 2013). It has been reported that there are vitamin D receptors in the hypothalamus and there is an interactions between vitamin D receptors and glucocorticoid receptors in the hippocampus. Depression has been associated with immune abnormalities (Yirmiya, 2000);hippocampal and glucocorticoids abnormalities. Taken together, evidence suggests that vitamin D might play a role in psychiatric illness such as depression (Berk et al., 2007; Black et al., 2003; Jorde, Sneve, Figenschau, Svartberg, & Waterloo, 2008; Penckofer, Kouba, Byrn, & Estwing Ferrans, 2010) .

The main source of vitamin D for humans is from its dermal synthesis by exposure to sunlight (Lips et al., 2014; Touvier et al., 2015) which provides up to 90% in the form of vitamin D₃ (cholecalciferol) with the remainder coming from food in the form of vitamin D₃ or vitamin D₂

(ergocalciferol) (Holick, 2004; Holick & Chen, 2008; LeBlanc et al., 2014; Umhau et al., 2013). Solar ultraviolet B radiation with a wavelength between 290 and 315 nm, penetrates the skin and converts 7-dehydrocholesterol to pre-vitamin D³, which then is isomerized by heat to vitamin D³ before being carried, bound to vitamin D binding protein, to the liver where it is converted into the main metabolite 25-hydroxyvitamin D₃. Prolonged sun exposure does not result in the production of excess quantities of vitamin D₃ to cause intoxication. Moreover, it has been argued that prolonged exposure can break down vitamin D, reducing health benefits and increasing risk of skin cancer (Annweiler et al., 2010; Berridge, 2015). Therefore, it has been suggested that moderate sun exposure is as effective as long sun exposure for previtamin D production (Annweiler et al., 2010; Cui et al., 2014)

While there is sufficient evidence of an association between low serum 25(OH)D and mood disorders such as depression (Bertone-Johnson et al., 2011; Jorde et al., 2008; Kerr et al., 2015), there is still a lack of studies on sun exposure, the main source of vitamin D in most countries. Given the limited research, the aim of this study is to investigate the association between past and recent sun exposure sun exposure (as a proxy for vitamin D status) and later depressive symptoms. Using a large, prospective, population based, cohort study, we tested the hypothesis that sun exposure behaviour predicts later depressive symptoms.

5.3 Methods

5.4 Measures

5.4.1 Assessment of Depressive Symptoms by a self-report questionnaire.

Depressive symptoms were assessed in this cohort with the reliable screening assessment for depression based on the DSM-5 criteria (American Psychiatric Association, 2013). Current National Institute for Health and Care Excellence (NICE) guidance uses the Diagnostic and Statistical Manual Fourth Edition (DSM-V) classification (<https://www.nice.org.uk/guidance/cg90>). According to the guideline, to diagnose major depression, this requires at least one of the core symptoms:

- 1) Persistent sadness or low mood nearly every day.
- 2) Loss of interests or pleasure in most activities.

The corresponding 2 questions were included in a self-report questionnaire assessing participants' attitude and feelings. Questions were answered with "Yes" or "No".

1-Have you ever felt sad, down or depressed two weeks or longer in a row?

2-Has there ever been a time period which has lasted two weeks or more, when you've lost all interest in most things in life, such as work, hobbies or some other occupation you usually enjoy?

The questions were translated from English into Swedish and back-translated to increase reliability to the original scale.

We considered the above two questions as two main outcomes of depressive symptoms. Both outcome variables are binary (Yes/No). Only women with non-missing data were included.

5.4.2 Sun Exposure

Sun exposure was measured by the following two variables:

HISTORY OF SUNBURN: For each 10 year age period (10–19, 20–29 and 30–39), the participants were asked to report the number of times per year they had been burned by the sun so severely that it resulted in pain or blisters that subsequently peeled by choosing from among five categories: never, one time per year, two or three times per year, four or five times per year, or six or more times per year.

SUNBATHING HOLIDAYS: Participants reported the average number of weeks per year spent on sunbathing vacations in Sweden or in southern latitudes (at this time typically southern Europe, e.g., Spain or Greece) or Sweden for each 10 year age period by choosing from among five categories: never, 1 week per year, 2–3 weeks per year, 4–6 weeks per year, or ≥ 7 weeks per year.

For each category of sun exposure history, we combined exposure across the three decades: 10–19 years, 20–29 years and 30–39 years. Thus, we created three categories for each sun exposure variable: Sunbathing holidays (Never; 1 week per year; ≥ 2 wks per year) and History of sunburn (None; 1 time; ≥ 2 times).

5.5 Confounders

Similarly to the previous study, lifestyle factors controlling access to sunbathing vacation and awareness of sun-protection as well as depression risk can be assumed depending on socio-

economic status and age. For this reason we considered years spent in education and attained age (in years) as possible confounders in all our analyses.

5.6 Statistical Analysis

We calculated summary statistics to compare women with different levels of sun-exposure on baseline characteristics (age and education, both continuous variables). We summarized the outcome variables related to depressive symptoms by plotting side-by-side bar segmented bar charts (two separated bar charts for each outcome). Each segment represents the level of the item (1=Yes and 2=No), the size of each segment in the figure is proportional to the number of women with this response.

5.6.1 Logit regression

Logistic regression, or a logit model, is used to model dichotomous outcome variables. In the logit model the log odds of the outcome is modelled as a linear combination of the predictor variables. A logistic regression model describes a linear relationship between the logit, which is the log of odds, and a set of predictors.

$$\text{Logit}(\pi) = \log(\pi / (1-\pi)) = \alpha + \beta_1 \cdot x_1 + \dots + \beta_k \cdot x_k = \alpha + x \beta$$

The association between sun exposure (sunbathing holidays and history of sunburns) and depressive symptoms ("Feeling unusually sad or down in the dumps" and "Lost interest in most things or activities once enjoyed") was summarised in terms of odd ratios (ORs) and corresponding 95% confidence intervals, and it was evaluated by age and education adjusted binary logistic regression using LOGISTIC procedure to model the analyses in SAS program version 9.4. For both sun exposure variables the intermediate and most common sun exposure ('1 week' for sunbathing holidays and or '1 time' for history of sunburns) were chosen as the reference category. The estimated associations given by a logistic regression are odd ratios (OR). Since the outcome status (namely depressive symptoms) among participants was unknown at study entry we cannot draw any conclusions about causality but only about the existence of associations (negative or positive). Based on the hypothesis under study we interpreted the $OR < 1$ as a negative association and $OR > 1$ as a positive association.

Missing values and dropouts due to a mechanism acting as a confounder between sun exposure and depressive symptoms and a not missing at random (MAR) could potentially bias the

results(Little & Rubin, 1987). We did not find any logical reason why this should be the case. Still, in a sensitivity analysis we addressed this potential problem by first comparing the covariate distribution among the women entering the cohort 1991 with the women returning for the follow-up. Inverse probability weighting (IPW) is one of several methods that can reduce this bias(Seaman & White, 2011). In this method, complete cases are weighted by the inverse of their probability of being a complete case. We applied this method.

Models adjusted for potential confounders, including education and age at baseline were fitted.

Statistical analyses were performed using the SAS version 9.4

5.7 Results

Among the 34 415 women included in the study, we had information on depressive symptoms for 34, 402 women (follow-up study). Participants with missing data on depressive symptoms were excluded from the analysis (n = 392). Thus, a total of 34, 010 women were included in the analysis.

Of 34, 010 Swedish women included in the analysis 16, 135 women (47%) responded positively to “Feeling unusually sad or down in the dumps”. Additionally, of 34, 010 women 12, 447 (37%) responded positively to the second question assessing depressive symptoms (“Lost interest in most things or activities once enjoyed”).

Baseline characteristics by the two predictor variables with three level group of sun exposure are presented in table 9.

Table 9 Cohort Characteristics by Levels of Sun Exposure.

Sun exposure	Cohort	Age M(SD)	Education* M(SD)
	<i>N</i>		
Annual cumulative number of weeks spent on sunbathing holidays:	33,481		
Never	3,894	41.7(5.7)	11.7(3.3)
1 per week	10,043	40.5(5.6)	12.4(3.0)
≥2 per week	19,544	40 (5.7)	12.6(2.9)
History of sunburns:	33,334		
None	2,652	41.8(5.8)	11.3(2.9)
1 time	18,593	40.6(5.7)	12.4(3.0)
≥2 times	12,089	39.5(5.7)	12.7(2.9)

Note 8 All values reported as mean (M) and Standard Deviation (SD).

*Average years spent in education

When filling in the questionnaire the women were between 30 and 50 years old (mean=40.4, Standard Deviation =5.7). The average number of years in education was 12.4 years (Minimum=0, Maximum=40; Standard Deviation =3.0).

Table 10 shows results of a logistic regression analysis for the association of depressive symptoms and sun exposure measures. The first model is a crude logistic univariate relationship of sun exposure (history of sunburns and sunbathing holidays) and depressive symptoms ("Feeling unusually sad or down in the dumps" and "Lost interest in most things or activities once enjoyed"). The results showed that having been sunburned more than twice a year, versus one time, increases the log odds of having depressive symptoms ("Feeling unusually sad or down in the dumps") by 1.23 (95%CI 1.17-1.28). For women reporting no history of sunburns versus one sunburn the association was inversed with depressive symptoms at OR being 0.84 (95%CI 0.77-0.91). In Model 2, age at baseline and years in education were added to the previous model. The adjusted model retained its independent significant OR for reporting history of sunburns more than twice a year, versus one time OR 1.22 (95%CI 1.16-1.27). The results revealed no statistically significant association between the sunbathing holidays and "feeling unusually sad or down in the dumps".

Similarly, history of sunburns (≥ 2 times vs 1 time) was significantly associated with depressive symptoms ("Lost interest in most things or activities once enjoyed") in unadjusted and adjusted models with OR being 1.17 (95%CI 1.11-1.22) and 1.14 (95% CI 1.09-1.19) respectively. Sunbathing holidays (≥ 2 weeks vs 1 week) was statistically significantly associated with "Lost interest in most things or activities once enjoyed" only in model 1, OR being 1.06 (95%CI 1.006 to 1.11), and at borderline significance after adjusting for age and education status (OR 1.050, 95%CI 0.998-1.105; $p=0.057$).

Table 10 Logistic Regression Analysis for the Association of Sun Exposure Variables with Two Outcomes Measures of Depressive Symptoms.

“Feeling unusually sad or down in the dumps”						
	Model 1			Model 2		
	OR	95% Wald Confidence Limits		OR	95% Wald Confidence Limits	
History of sunburns						
(≥2 times vs 1 time)	1.231	1.176	1.289	1.216	1.161	1.274
(None vs 1 time)	0.844	0.777	0.917	0.891	0.819	0.969
Sunbathing Holidays:						
(≥2 weeks vs 1 week)	1.043	0.994	1.095	1.041	0.991	1.093
(Never vs 1 week)	0.931	0.865	1.003	0.978	0.907	1.055
“Lost interest in most things or activities once enjoyed”						
History of sunburn						
(≥2 times vs 1 time)	1.167	1.113	1.223	1.143	1.090	1.199
(None vs 1 time)	0.946	0.868	1.030	0.975	0.893	1.064
Sunbathing Holidays:						
(≥2 weeks vs 1week)	1.058	1.006	1.112	1.050	0.998	1.105
(Never vs 1 week)	1.028	0.952	1.110	1.073	0.993	1.161

Note 9 Only the ORs in bold are of statistical significance.

OR = Odd ratios

Model 1 = Unadjusted

Model 2 = Adjusted for age at baseline and years in education

We predicted probabilities of participating in the follow up part of the study based on subject characteristics. After applying the weights to the logit regression models, we concluded that the estimates did not differ from the original estimates

5.8 Discussion

Sun exposure is the most important source of vitamin D. In a population based cohort of 34,010 women we found that history of multiple sunburns was associated with depressive symptoms. It is worth noting the prevalence of depressive symptoms in this sample (47% and 37% responding positively) is relatively high.

The results revealed an association between multiple sunburns and depressive symptoms however the same association is not evident for sunbathing holidays and depressive symptoms. Further, no sun exposure is not associated with depressive symptoms. Biologically, the sunburns caused by exposure to UV radiation should produce vitamin D. However, the extensive exposure to UV could produce too much vitamin D which might induce negative health outcomes (more depressive symptoms). In fact, exposures to the sun can break down vitamin D and reduce health benefits, for example according to our study the overexposure could increase depressive symptoms. Alternatively, women who experienced multiple sunburns after UV exposure might exhibit a tendency to more risky behaviour. Although this association is evident in this population, the reasons why the women with more depressive symptoms would experience more sunburns compared with the rest of the population are unclear. Else, the observed association might represent self-medication— i.e. sun exposure produces vitamin D thus could improve the mood and provide many positive health outcomes or simply relieves boredom or distress (an assumption of the more sunshine the more vitamin D and enhanced health benefits) which could, in fact, indicate reverse causality.

No earlier studies that we are aware of have evaluated the relationship between different life periods sun exposure and vitamin D levels and depressive symptoms. The findings from my study contradicts previous work on sun exposure, vitamin D and health outcomes. For instance, one study found that there was no close association of vitamin D levels with depression (Knippenberg et al., 2014). Interestingly, when sun exposure was taken into account, this association was no longer statistically significant indicating that sun exposure has a more potent effect on depression which is independent of vitamin D synthesis (Knippenberg et al., 2014). Another study by Wilkins et al 2006 examined the relationship between vitamin D status, cognitive performance, mood, and

physical performance in older adults. Their findings showed that vitamin D deficiency was associated with low mood and with impairment on some measures of cognitive performance (Wilkins et al., 2006).

The present study examined the sun exposure variables considering sun exposure as a main source for vitamin D levels and not diet (Holick, 2004; LeBlanc et al., 2014; Umhau et al., 2013). In terms of confounding variables we controlled for age at baseline and years spent in education. Studies showed that these are the main demographic variables associated with depressive symptoms in a general population (Henderson & Pollard, 1992).

Consequently, a major strength of our study is the detailed assessment of sun exposure during different periods of life. The information on sun exposure habits was gathered at the start of the study which minimizes the risk of reverse causality. Another major strength of this study is use of an unselected large population-based cohort drawn from the Swedish National Population Register and followed for over 10 years.

As explained above, this study found the opposite link to what was expected. However, there are many important limitations to this study. This includes the possibility that other health and lifestyle factors are influencing the link.

The results of this study must be interpreted in light of limitations associated with a structured interview and the potential for participants' response bias. The questionnaire-based assessment of sun exposure was possibly prone to measurement error. Also, data on sun exposure was collected retrospectively. Recall bias might result in either an underestimate or overestimate of the association between sun exposure and the outcome. However, the recall bias (if present) should not have a differential effect (i.e., those with more psychotic symptoms remember more exposure and those without psychotic symptoms remember less) on the study, and therefore, results should not be systematically biased.

Further, we had no biological data on vitamin D levels, which could have established a clear link to vitamin D and yet it is well known that sun exposure is the most important determinant of vitamin D status (Holick, 2004; LeBlanc et al., 2014). Additionally, the assumption was made that sun exposure habits did not change over time and consequently, information from one assessment alone was used in the models. This is a common assumption in cohort studies and tends to underestimate risk. However, the questionnaire took into consideration changes, as it asked about exposure in different decades.

The current study was based on multiple exposure factors (several sun exposure variables) as proxies for vitamin D level and their relationship with depressive symptoms. The estimates were adjusted for confounding effects and each exposure variable was assessed independently in order to detect any potential effect. Still, our results should be interpreted cautiously. Even well-designed observational studies can be influenced by residual confounding. There may also be a number of unknown factors that we did not take into consideration in our study, which could influence depressive symptoms and be related to sun exposure.

Moreover the assessment of depressive symptoms included only two questions however the questions were based on the diagnostic criteria DSM-5. This form of assessment of depressive symptoms in the general population was not previously validated in this cohort

In terms of generalizability of the study, males were not included. Previous research showed that female gender was significantly associated with depressive symptoms (Doğan et al., 2011; Ford & Erlinger, 2004). The study showed that prevalence of a major lifetime depression among 6914 young US adults from the NHANES-III survey was higher for women than men (5.7% in men and 11.7% in women). Epidemiological findings point to a female gender in prevalence of depressive symptoms (Piccinelli, 2000).

5.8.1 CONCLUSION

High sun exposure (history of sunburns) vs intermediate exposure is associated with some symptoms of depression, in particular with feeling sad or depressed and lost interest in most things or activities once enjoyed. Previous studies have reported relationships of vitamin D with increased risk for health problems, such as depression, as well as clinical symptoms in patients with mental health problems. However, there is a lack of previous studies on how sun exposure, the main source of vitamin D, influences depressive symptoms in the general population. This study's contribution to the literature is that in the general population of middle-aged Swedish women high vs intermediate sun exposure is positively associated with main symptoms of depression.

Chapter 6 General Discussion

This section will summarize and integrate the findings from the studies presented in chapter 3-5. While above evidence and other data suggest PUFA and/or vitamin D imbalance may be a risk factor for schizophrenia, depression and cognitive decline, their role in the onset of psychotic or depressive symptoms remain uncertain and their biological mechanism are not well understood. Further investigations of a possible relationship between nutrients status in cognitive development, psychotic and depressive symptoms is required. Indeed psychiatric conditions and cognitive disturbances involve so much more than PUFA or vitamin D imbalance yet there is some evidence for these nutrients being related to cognitive impairments and mental health. There is no definitive approach to examine nutrition and its effect on neurodevelopment or late mental health therefore the assessment could only take place through lifespan examination.

This thesis has the following specific aims:

- 1) Determine the association between prenatal fish oil intake and the offspring cognitive abilities with focus on general and specific cognitive abilities using a Meta-Analysis approach
- 2) Examine if there is an association between UV exposure, vitamin D and psychotic experiences in adult Swedish women
- 3) Determine if there is an association between UV exposure, vitamin D and depressive symptoms in the adult Swedish women.

Aim 1 was examined using a Meta-Analysis; data for Aims 2 and 3 comes from the Women Lifestyle and Health Study, a population based longitudinal study of Swedish women.

6.1 Summary of findings

6.1.1 Fish Oil and Fish Intake during Pregnancy and Cognitive Functioning In Offspring: Systematic Review and Meta-Analysis of Randomised Control Trials and Observational Studies

In the first study, I demonstrated that that prenatal fish oil or fish intake was associated with better cognitive abilities in the offspring. I found concordance across reviewed study designs where randomised control trials supported the results of the observational studies on this topic. Evaluations of eight randomized control trials found the results approaching statistical significance towards better cognitive functions among children of mothers in fish oil intervention group. Examination of specific cognitive outcome showed that fish oil was particularly beneficial for memory functions. Analyses of observational studies suggest that consuming fish 2-3 times a week, which was the most common category of fish consumption by pregnant women in the selected studies, is beneficial for optimal cognitive development of the offspring specifically for domains related to language and verbal skills.

6.1.2 Sun Exposure, Vitamin D and Psychotic Experiences

The results from this study showed that, in the Nordic countries, as elsewhere, where sun exposure is the most important source of vitamin D, in a population based cohort of 34,402 women, there was an association between cumulative measures of sun exposure (sunbathing holidays and history of sunburns) at ages 10 to 39 years and positive psychotic experiences. I observed a U-shaped association where women with low sun exposure as well as women with high sun exposure reported more psychotic experiences compared to women with an intermediate level of sun exposure.

6.1.3 Sun Exposure, Vitamin D and Depressive Symptoms

Unexpectedly, the findings from this study revealed that cumulative measures of sun exposure (history of multiple sunburns) at ages 10 to 39 years was associated with some depressive symptoms in the population of adult Swedish women. In this study a high proportion of women reported depressive symptoms described as feeling unusually sad or lost interest in most things, or activities once enjoyed.

6.2 Strengths and limitations

6.2.1 Strengths

The key strength of this thesis is the evaluation of nutrients across lifespan (from pregnancy to adulthood). Starting with the Meta-Analysis, by combining studies, any Meta-Analysis increased the sample size and thus the power to study effects of interest. Some research suggest that meta-analyses should be conducted only on randomized controlled trials as meta-analyses should include only reasonably well-conducted studies to reduce the risk of a misleading conclusion. However, many important conditions can only be studied observationally. The Comprehensive Meta-Analysis and systematic review methods allowed me to compare the effects from randomised control trials and observational studies and strengthen the conclusion of prenatal fish oil and fish intake as potential enhancement for the offspring cognitive abilities. Another strength of this study is the fact that the study examined specific and overall cognitive domains and therefore methodically evaluated a complete neuropsychological profile in the offspring of mothers supplemented with fish oil or those who consumed fatty fish enriched in omega-3.

Further, strengths of the studies related to the UV exposure and mental health outcomes include the access to high quality data, its large size, prospective design, and virtually complete follow-up through linkages to national registries. The large sample size of over 30 000 women provides the statistical power to investigate the outcomes. The information on UV exposure at different periods in life and relevant data on host characteristics and lifestyle factors is also an important strength. The Women Lifestyle and Health study contain detailed information on individual characteristics important in our analyses. The data in longitudinal cohort designs is normally collected for reasons independent of both the exposure variables (sun exposure) and the outcome

variables (psychotic experiences and depressive symptoms). A main strength of the cohort is that follow-up of the women is based on the unique national registration number, allowing linkage to a broad range of validated Swedish registries that include information on things such as cause and date of death, hospital discharge and drug use. Reporting is mandatory for several of these registries and, as mentioned previously, the validity of Swedish registries has generally been found to be high (Barlow, Westergren, Holmberg, & Talbäck, 2009; Roswall et al., 2015).

The information include confounders such as age, education, alcohol intake and important information related to sun sensitivity characteristics which I explored in sensitivity analysis. This has allowed me to perform our analyses with detailed adjustments for possible confounders.

Further, the ethnic homogeneity of our study population reduces the risk of confounding by unmeasured factors, both genetic and environmental.

Additional study's strength was a detailed assessment of sun exposure between age 10-39 including both sun exposures in southern latitude and in Sweden. A strong association between the UV exposure questionnaire and risk of malignant melanoma shown in previous analyses from the same cohort (Yang et al., 2011) suggested that those questions assessing sun exposure are appropriate.

No earlier studies that we are aware of have evaluated the relationship between sun exposure, vitamin D and psychotic symptoms in adult life. The present study examined the sun exposure variables considering sun exposure as a main source for vitamin D levels and not diet. Sunlight is the superior source for vitamin D, as when you expose your skin to sunshine, your skin synthesizes vitamin D3 sulphate. This form of vitamin D is water soluble, unlike oral vitamin D3 supplements, which is unsulphated. The water-soluble form can travel freely in your bloodstream, whereas the unsulphated form needs LDL (the so-called "bad" cholesterol) as a vehicle of transport.(Mercola, 2011). The oral non-sulphated form of vitamin D may not provide all of the same benefits as the vitamin D created in your skin from sun exposure, because it cannot be converted to vitamin D sulphate.

We have utilised appropriate modern statistical methods. These include the use of Comprehensive Meta-Analysis. Meta-Analysis itself can address possible power issues in under-powered studies. We used advanced epidemiological and statistical methods; data was manipulated in SAS program and the use of a quantile regression allowed to examine the functional form of continues variable (psychotic symptoms). Statistical methods are however not an independent component in epidemiological research but a bidirectional process: high quality

data supports the use of advanced statistical methods, and knowledge of statistical methods is a key when deciding what data to use.

6.2.2 Limitations

The presented studies do have some limitations. My Meta-Analysis integrated studies that used various cognitive tests, assessment were made at different age the randomised control trials varied in terms of the dosage. However I performed a meta-regression of DHA dosage in randomised control trials and did not find statistically significant results. Further, a meta-regression of the effect of 'age at assessment' on cognitive abilities revealed no statistically significant moderating effect.

Overall, the Women Lifestyle and Health cohort is limited by the potential healthy volunteer bias, as those with a serious illness or disability might be less likely to participate both at baseline and at follow-up. As explained in the description of the cohort (Roswall et al., 2015) the healthy volunteer bias is stronger in the selection of women who responded to the follow-up questionnaire. This can contribute to the generalizability of findings from the WLH study. All information collected in the questionnaires is self-reported, and information about the exposure and the outcomes of the present study is self-measured, leaving room for potential information bias. However, no validation studies have been conducted on information collected in the sun exposure and mental health questionnaires and this should be kept in mind when interpreting these data. Further, data on sun exposure was collected retrospectively, and recall of events from a few decades back could be biased.

Our results of a protective effect of the sunshine and vitamin D in association with psychotic experiences must be considered as rough, since we only measure the cumulative sun exposure as a proxy for vitamin D. A more complete picture of the vitamin D status could have been supplied through vitamin D levels in blood; however, biological samples are not available.

One of the limitations of this thesis is that in the study on sun exposure and psychotic experiences we have no baseline measures of symptom levels to further reveal causality between different levels of sun exposure and the association with positive psychotic symptoms. However, considering the prevalence results for psychotic disorders, fairly small number of participants in the population sample are likely to have a psychotic disorder, which might increase the problem of reversed causality related to psychotic diagnosis or medication.

In the studies looking at the UV exposure and mental health outcomes we had no information about socioeconomic status, but the adjustment for education, which is strongly associated with socioeconomic status, did not change the estimates. However, we cannot rule out that there are unknown confounders that have not been adjusted for.

We compared a number of characteristics for participants who completed the questionnaire, both in the baseline study and the follow-up study, with those who only answered the questionnaire in the baseline study. Age and the education did not differ significantly between those who participated in the follow-up study and those who did not (drop-outs). The drop-outs had a slightly lower education. However, our main exposure sun exposure did not differ between those who participated and those who did not participate in the study.

Overall limitation of this thesis is lack of data on nutrition in adolescence period thus it limits our conclusion of nutrition and its role across the entire lifespan. We explored a prenatal omega 3 intake and children neurodevelopment and the Women Lifestyle and Health study provided me with a high quality data in order to explore the mental health outcomes in adulthood. Nevertheless the Swedish cohort allowed me to explore the sun exposure and vitamin D reports from as early as at age 10 which is also a critical period for an optimal brain development.

Another shortcoming of the thesis is a lack of examination of a comprehensive set of outcomes. Other important outcomes such as cognitive functioning in adulthood, aging and other mental disorders were not examined

6.3 Integration of findings and comparisons with earlier research

The results and conclusions of this thesis contribute to earlier research in several important ways.

Fish Oil and Fish Intake during Pregnancy and Cognitive Functioning In Offspring: Systematic Review and Meta-Analysis of Randomised Control Trials and Observational Studies

There has been considerable attention to the potential role of fish oil supplementation and oily fish intake during pregnancy and their link to the offspring's cognitive abilities but with conflicting results. We summarised and integrated this information in a systematic way. In a Meta-Analysis we combined already published studies including both randomised control trials (supplementation with fish oil) and observational studies (fish intake during pregnancy). The randomized controlled trials showed better cognitive abilities in children of mothers in fish oil supplementation group. For the measure of overall cognitive ability the standardized difference in means (SMD) was estimated to 0.10 (95% CI, -0.01 to 0.20; $p=0.07$) and for memory functions the SMD was 0.21 (95% CI, 0.01 to 0.41; $p=0.04$). The observational studies showed better overall cognitive ability with pooled OR of 1.92 (95% CI, 1.61 to 2.30; $p<0.001$) and for the domain of language and verbal skills the OR was 1.93 (95% CI, 1.37 to 2.73; $p<0.001$) among children of mothers consuming 2 to 3 fish servings per week during pregnancy. We evaluated cognition in a context of overall and specific cognitive abilities. The overall consistency of our findings, regardless of study type, is reassuring.

Overall, one explanation for the heterogeneity of individual study results is that the discrepancies between observational studies and interventional studies might be due to the fact that omega-3 PUFA in fish is more bioactive than fish oil in a form of supplementation. Also, socioeconomically advantaged pregnant women are more likely to have better balanced diet. According to the previously published study, apart from omega-3 PUFA, fish consist of other beneficial nutrients (i.e. selenium, vitamin D, iodine) and these might play an important role in enhancement of cognition (Nesheim & Yaktine, 2007). Epidemiological studies are generally better powered but they might also potentially have less control for confounding. However, by integrating both designs we resolved the inconsistency of the findings and our Meta-Analysis confirmed the beneficial effect of prenatal omega 3 PUFA intake and this is in accordance with most

observational studies (Daniels et al., 2004; Oken et al., 2008). This thesis supports the large data published earlier from the Avon Longitudinal Study of Parents and Children (ALSPAC) in the UK regarding fish consumption and child cognitive development (Daniels et al., 2004; Hibbeln et al., 2007). These studies found data that higher maternal fish consumption was associated with higher language (after appropriate adjustments) in 7421 British children assessed at 15 months, using the MacArthur Communicative Development Inventory (MCDI), and at 18 months using the Denver Developmental Screening test. The later ALSPAC study demonstrated that those children whose mothers consumed less seafood during pregnancy had lower IQ, measured by the Wechsler Intelligence Scale for Children III (WISC-III) at the age of 8 (after adjusting for a wide range of relevant covariates). Lower maternal seafood consumption was also linked to suboptimal language development (measured using the Denver Developmental Screening test) at six, 18, 30, and 42 months of age in the same study (Hibbeln et al., 2007).

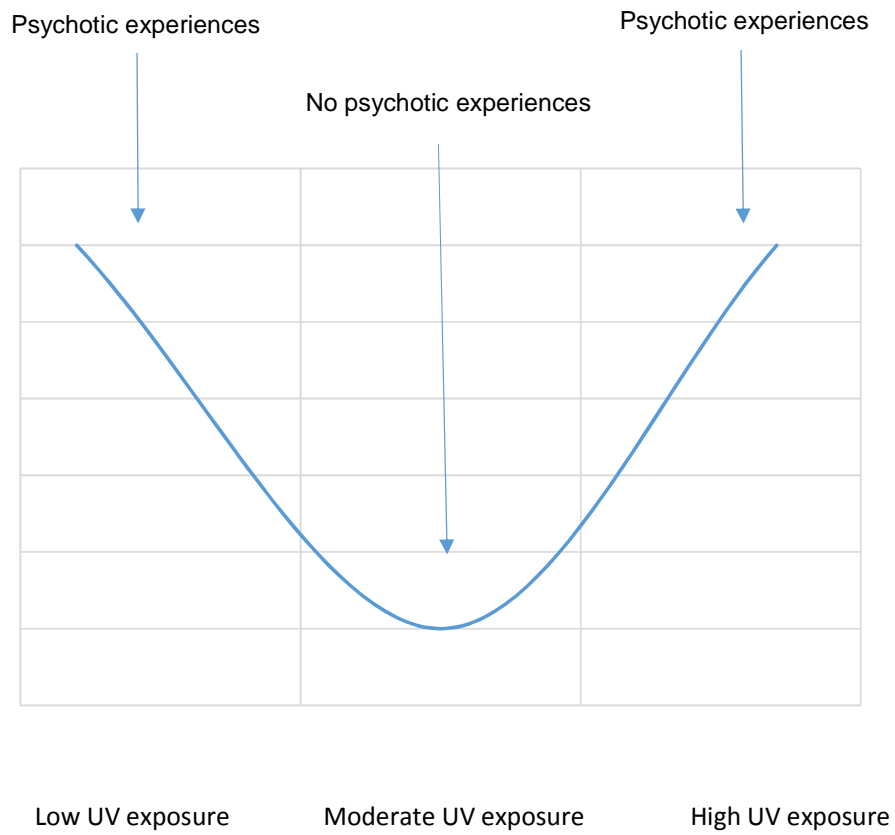
Our results agree with what is expected following integration of the research and showing a stronger effect in epidemiological studies. In this up to date review and meta-analysis of all available literature, we found that prenatal fish oil was associated with better cognitive abilities in the offspring. We found concordance across reviewed study designs where randomised control trials supported the results of the observational studies.

Sun Exposure, Vitamin D and Psychotic Experiences

First we showed that compared with women who reported a history of one sunburn, the women with 'None' or ≥ 2 sunburn showed higher scores on the CAPE scale with more women in the right part of the distribution. Similarly, compared with women exposed to 1 week of sunbathing holidays, the women with none or ≥ 2 weeks showed higher scores on CAPE scale. The results were statistically significant across the entire distribution of the CAPE scale.

The above results are novel as no study has previously considered an examination of UV exposure with relation to psychotic experiences in a general population. We observed a U-shape relationship in the cohort of adult Swedish women illustrated below.

Figure 16 U-shaped relationship between different levels of sun exposure and psychotic like experiences.



Our results agree with the study published in JAMA that reported a similar U-shaped association examining risk for schizophrenia however the authors measured vitamin D levels in blood. They found that both low and high concentrations of neonatal vitamin D in Danish cohort are associated with increased risk of schizophrenia (J. J. McGrath, Eyles, et al., 2010).

Our results are also in line with a longitudinal, nested case-control study in the Nordic countries reported a U-shape relationship between vitamin D levels and health outcomes. However, it was evaluated for a cancer risk not mental health outcomes. The study revealed that both high and low levels of blood vitamin D are associated with a higher prostate cancer risk (Tuohimaa et al., 2004).

This thesis and above mention studies that reported U-shaped associations between vitamin D and health outcomes (illustrated in figure 16) might be a potential indication for the fact that optimal levels of vitamin D and/or sun exposure are beneficial regardless of the health outcome. This non-linear association is evident especially in Nordic populations examining mental health

outcomes. However, the associations with dietary components and health are often non-linear with advantageous effects of a balanced nutrition.

Concerning the impact of low vitamin D on the adolescent and adult brain and psychotic symptoms, a recent study based on a population-based birth cohort from South West England - ALSPAC, (n = 3,182), found an association between low vitamin D during childhood (mean age 9 years) and an increased risk of psychotic symptoms during adolescence (mean age 14 years) (A. M. Tolppanen et al., 2012). A large population-based study of the same cohort of Swedish women as ours (n = 33,623) found a significantly increased risk of psychotic experiences in those with low vitamin D intake from diet (Hedelin et al., 2010). Thus, our evidence enhances the knowledge that low sun exposure and low vitamin D not only disrupts early brain development but may also compromise later periods of brain growth and maturation and contribute to later mental health problems.

The public health implications of our findings are ambiguous as long as the underlying mechanism is unclear. The highest UV exposure in our study were far below the exposures which would generally be perceived as harmless, and we find it unlikely that the association between these higher sun exposures and increased psychotic experiences reflects a direct harmful effect of vitamin D. However, this study indicates that complex biological mechanisms are involved in the relationship between sun exposure, vitamin D and psychotic experiences in adult women, suggesting that recommendations of sun exposure in order to keep the optimal level of vitamin D should be considered with caution.

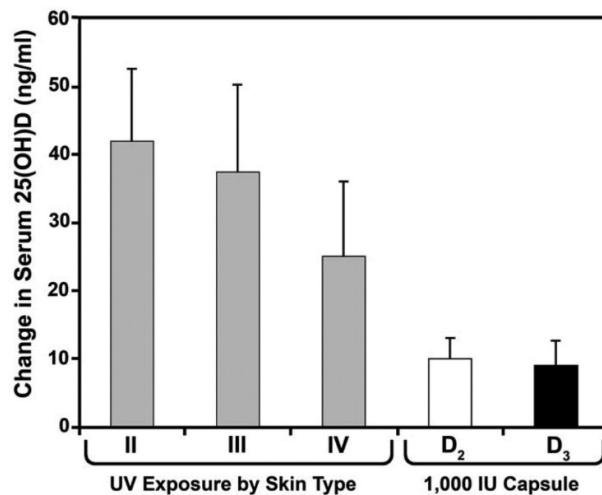
This research does seem to show that there is a link between vitamin D from sun exposure and psychotic symptoms. However, we don't know exactly what that link is. Research has not yet clearly shown whether low levels of vitamin D cause psychotic symptoms, or whether such symptoms cause low levels of vitamin D. This means that we are unsure whether taking a vitamin D supplement, or getting more vitamin D by exposing the skin to the sun, will help to prevent or ease the symptoms of psychotic symptoms or other mental health problems in some people.

The adverse effects of UV radiation are easy to see but the beneficial effects are difficult to determine as they occur after many years, and might be influenced by other factors such as age, diet, smoking, etc. However, the health benefits are much stronger (Grant, 2009).

Keeping in mind the review literature and the current study, there are a number of reasons why public health policies regarding UV irradiance and vitamin D are not where they should be. For

instance, the sunscreen industry proposed the idea that people should avoid the sun and apply the sunscreen before exposing to the sun. Consequently serum vitamin D concentrations have decreased globally (Grant, 2009). As mentioned in my introduction, moderate degree of UV exposure is necessary for the production of Vitamin D which is essential for physical and mental health. The findings from the present study provided additional evidence to support this-women with moderate sun exposure reported no psychotic experiences. Additionally, evidence emerges that low Vitamin D levels are likely to be associated with many chronic diseases. Considering a U-shaped association presented in this thesis and supported but other studies with vitamin D and mental, and physical health outcomes, public health policy on ultraviolet radiation needs to aim at preventing the disease burden associated both with excessive and with insufficient UV exposure.

Further, our study used UV exposure as a main proxy for vitamin D levels as we believe this is the only valid source of vitamin D synthesis in humans. Because foods contain very little vitamin D it is difficult to obtain enough vitamin D from dietary sources even when consuming foods fortified with vitamin D. There has been a lot of discussion amongst researchers as to whether consumption of vitamin D from the diet or in a form of a supplement is the same as producing vitamin D₃ in the skin when exposed to UVB. Because it takes approximately 8 h for previtamin D₃ in the skin to fully convert to vitamin D₃ and it takes additional time for the vitamin D₃ to enter the dermal capillary bed this is at least 2 of the explanations for why it was observed that vitamin D₃ produced in the skin last 2–3 times longer in the circulation when compared with oral consumption (Haddad, Matsuoka, Hollis, Hu, & Wortsman, 1993). Furthermore when vitamin D₃ is produced in the skin 100% of it is potentially bound to the vitamin D binding protein. When vitamin D₃ is consumed in the diet or supplement it gets combined to chylomicrons which are transported into the lymphatic system and then into the venous system were approximately 60% of the vitamin D₃ is bound to the vitamin D binding protein and 40% is rapidly cleared in the lipoprotein bound fraction (Haddad et al., 1993).



Note 10 D₂=Vitamin D2 and D₃=vitamin D3

Note 11 Skin type II, III and IV

The above figure 17 shows the importance of UVB exposure in vitamin D production. The figure presents a comparison of the percentage increase in serum 25(OH)D levels of healthy adults who were exposed to UVB radiation once a week for 3 months in a bathing suit of with healthy adults who received either 1000 IU of vitamin D2 or 1000 IU of vitamin D3 daily during the winter and early spring for a period of 11 weeks. The study showed that fifty percent increase represented approximately 10 ng/ml from baseline 18 ± 3 to 28 ± 4 ng/ml. in this study, skin type is based on the Fitzpatrick scale: Type II always burns, sometimes tans; type III always burns, always tans; type IV sometimes burns.

It is possible that the accumulated exposure to sun over the life-course could result in brain alterations. Those with little or lack of sun exposure and those with the highest range of sun exposure reported psychotic experiences. Insufficiency of sun exposure produced less vitamin D resulting in more psychotic experiences. A similar pattern was observed for high sun exposure which could be a result of toxicity of vitamin D. However the literature on vitamin D states that hypercalcemia (toxicity due to high levels of vitamin D) is not a result of vitamin D from sun exposure or food but supplements only. Almost all vitamin D overdoses result from taking high amounts of vitamin D supplements. It is almost impossible to get too much vitamin D from sunlight or food. However, it can be speculated that overexposure to sun could break down vitamin D and reduce health benefits similarly to a low or lack of sun exposure.

Sun Exposure, Vitamin D and Depressive Symptoms

Further investigation of sun exposure and mental health outcomes related to depressive symptoms in the Swedish cohort revealed that too much sun could result in occurrence of depressive symptoms in this particular sample of adult Swedish women. Women with multiple sunburns showed higher odd ratios for depressive symptoms. These results are partially comparable with the findings from the study above examining sun exposure and psychotic symptoms. It's worth noting that in both these studies high exposure was associated with poorer mental health-reports of psychotic experiences and depressive symptoms. In the depression study, however, the association was evident only for multiple sunburns and not sunbathing holidays variable.

Firstly, there is not a single study that examined the association between sun exposure and depressive symptoms in a general population. Secondly, the results from our study differ from previously published literature on vitamin D levels and depressive symptoms. For example, findings from one population based study supported a potential inverse association of vitamin D from food sources, and depressive symptoms in postmenopausal women (Bertone-Johnson et al., 2011). Contrary to the results of my study, findings from the ALSPAC study showed that higher concentrations of 25(OH)D₃ assessed at mean age 9.8 years were associated with lower levels of depressive symptoms at age 13.8 years. A recent review by Anglin et al 2013 on vitamin D and depression looked at the all published good quality research studies that tested whether a lack of vitamin D in human's blood is linked with being depressed or whether a lack of vitamin D in blood makes it more likely to develop depression (Anglin et al., 2013). These results were contrary to our findings on sun exposure and depressive symptoms indicating that there is a relationship between low levels of vitamin D in the blood and depression. A key message from an existing literature on vitamin D levels in blood and depression is that research does seem to show a link between low levels of vitamin D in the blood and symptoms of depression (Anglin et al., 2013; Berg et al., 2010; Jorde et al., 2008; Wilkins et al., 2006). Considering the results of our study on sun exposure as a proxy for vitamin D levels, the association is contradictory - the more sunburns the more depressive symptoms in the cohort of Swedish adult women.

From a behavioural point of view, several theories could be applied as potential explanation for the opposite association we found, one of them focused on self-medication theory explained earlier in chapter 5. In short, possible reasons for taking up too much sun could be related to self-medication, the more sunshine the better health outcomes. Therefore women from the cohort could overexposed themselves to sun in order to improve their mood. Alternatively, women with more sunburns and depressive symptoms could exhibit patterns of high-risk behaviours, i.e. they have tendency to spend extra time in the sun until their skin burns. There is a strong relationship between depression and high-risk behaviours.

With current knowledge, biological explanation for this positive association between multiple sunburns and depressive symptoms is challenging. Some of the common symptoms of vitamin D overdose characterize depression. However, even for the women in our cohort who reported an overexposure to UV, it would be impossible to reach a toxic level of vitamin D. It is widely accepted that vitamin D produced in the skin as a result of sun exposure “is not known to result in toxic levels” (Blake, 2008). This is because levels produced in the skin are self-adjusting based on the body's needs.

However as far as we are aware, this is the first study showing a positive relationship between sun exposure and depressive symptoms and found no association between potential vitamin D deficiency and risk for later depressive symptoms. This does not rule out the fact that in already depressed cases there will be low levels of vitamin D and that vitamin D supplementation in depressed individuals will be effective. Moreover, it should be noted that the present study is a study of depressive symptoms and perhaps the association with symptoms is not the same as with the clinical conditions, this should be consider in other studies. As a comparable example, some studies show a link between psychotic symptoms and cognitive normalization in childhood while other showed psychotic illness being associated with increasing impairment (Reichenberg, 2005).

6.4 Future directions

This thesis presented the importance of nutrition (omega-3) in early neurodevelopment and later impact of nutrition (vitamin D measured by sun exposure behaviours) on mental health outcomes in adults (positive psychotic experiences and depressive symptoms). Although the aetiology of mental health is complex, the emerging and convincing indications for nutrients as an important factor for the high prevalence and incidence of frequent mental problems, such as depression or schizophrenia indicating that balanced diet is as important in psychiatry as it is in other physical conditions such as cardiovascular disease or endocrinology. At the population level, we had scientific evidence that optimal sun exposure and vitamin D is associated with a lower incidence of positive psychotic symptoms and meta-analysis of RCTs and OS showed that prenatal omega-3 especially DHA levels are associated with enhanced cognitive abilities.

Firstly, focusing on omega 3, future studies should consider a recommended prenatal omega 3 dosage and oily fish servings according to health governance recommendations to obtain any health benefit and enhance children cognitive abilities. At this stage it was difficult to conclude from the existing literature due to too many inconsistencies in prenatal dosage of omega 3. Also, a potential issue could be inconsistent measurements of children cognition. There is need for standardised assessments to adequately evaluate children cognitive development. This could also allow more reliable meta-analysis evaluation.

Since animal studies have demonstrated that deprivation of omega-3 fatty acids during pregnancy is associated with behavioural deficits that cannot be reversed with postnatal supplementation (Coletta, Bell, & Roman, 2010), for these reasons, it is important for omega-3 fatty acids to be supplied to the fetus in adequate amounts throughout pregnancy. To optimize pregnancy outcomes and fetal health, consensus guidelines have recommended that pregnant women consume at least 200 mg of DHA per day. A woman can achieve this threshold by consuming 2 to 3 servings of oily fish per week, dietary intake that is consistent with the current US Food and Drug Administration (FDA) and Environmental Protection Agency (EPA) advisory (Center for Food Safety and Applied Nutrition, 2014)

In my research I have relied on the use of national registers which helped to get around several problems present in clinically based samples. However there is a lack of data connecting these

observations to the underlying biology. For this reason initiatives to enrich the register data with biological data would be valuable (vitamin D levels).

Up to date, there is no a single cohort to answer all the questions. The main conclusion that I take away from this thesis is that research on vitamin D deficiency and its link to psychosis is at a very preliminary stage. There is a need for more research in this area – particularly that addressing the potential use of vitamin D supplements therapeutically and the specificity of vitamin D deficiency to psychosis over other diagnoses.

In this thesis the results of vitamin D from sun exposure and depressive symptoms analyses were somewhat contrary to previous studies. Further studies are needed to replicate these findings, preferably measuring blood levels of vitamin D in addition to sun exposure and there is a need for clinical trials including patients with clinical depression.

It is difficult to expect that anyone affected with mental health problems would improve only with medicines. Anyone would argue that the forthcoming research in psychiatry requires a broader approach in which nutritional factors are vital to provide better functioning and quality of life.

As stated by Cannel et al, “epidemiological evidence suggests that mental illness has increased as humans have migrated out of the sun and into buildings, cars, and sunblock” (Cannell et al., 2006).

We recommend for future prospective studies and randomized control trials to establish if the improvement of vitamin D status holds promise for the prevention of psychosis and/or depression, the treatment of it, or both.

At present, there is still some evidence that does not support a role of vitamin D in adult mental health problems such as our study of vitamin D and depressive symptoms which makes vitamin D deficiency a more probable consequence than a cause of depression. Consequently, it's acceptable to be sceptical for now as where research is available, it is limited and conflicting.

What is needed is more involvement and more research pushing the development of this field further. Other authors (D. W. Eyles, Burne, & McGrath, 2013) have outlined a feasible and persuasive argument for the role of vitamin D in the development of psychotic symptoms and in accordance with the previous findings in this thesis we argue that, indeed, a similar conclusion could be drawn in the general population of adult Swedish women when under or over-exposed to the sun. However the vitamin D field in mental health research have been held back by the lack of well-designed studies.

Adjusted, standardized, pooled analyses would help clarify shape of vitamin D-psychotic symptoms association. Currently, the shape of the association from the published literature is variable for example, our study revealed a possible U-shaped relationship. There is an urgent need to explore the mechanisms underlying the U- shaped curve in both clinical and general population

To our knowledge, this is the first study of its kind to explore the association between nutrition and mental health in children and adults; however, we acknowledge that further studies that contribute to a stronger level of evidence are required. We recommend that the relationships between both poor nutrition and poorer mental health and good nutrition and better mental health be examined using longitudinal study designs.

Prospective and intervention studies are now required to improve the level of evidence. Given that roughly half of all lifetime mental disorders in most studies start by the mid-teens and three-fourths by the mid-20s (Kessler et al., 2007). The potential for early intervention using strategies targeted at improving nutritional intake at a population level may be of substantial public health benefit.

A good designed study to evaluate the relationship between nutrition (vitamin D and omega 3, for example) and development of mental health illness would be a prospective birth cohort with measurements of biological samples of vitamin D levels and micronutrients from diet at early age and assessment of psychotic and depressive experiences in early adolescence and adulthood. In the present study we were able to access data only for early developmental period and late adulthood. For example if psychotic and depressive symptoms are related to the development of schizophrenia or depression, this would support a possible protective association of higher vitamin D concentrations with schizophrenia and mood disorders. Further, as it is not possible to combine biological or dietary vitamin D intake and sun behaviour into a single exposure variable as their methods of assessment are very different, a suggestion for a well-designed future study is to collect biological measures and vitamin D from diet, and sun behaviour data in order to run adjusted analysis. If the results show a positive association, then it could be argued that the sun behaviour variables are associated with psychosis independently of dietary or biological vitamin D levels. Such a result would strengthen the conclusions of the present study as it would have shown that two or three separate ways of measuring vitamin D status have the same relationship.

Moreover, adding prescription data would be advantageous to further validate symptoms of interest (unfortunately this was not feasible for the present study considering my PhD time frame).

Further, it would be of interest to study if nutrition such as omega 3 and vitamin D are associated with separable latent dimensions of positive psychotic symptoms or depression and if the associations are valid for men and for other age groups.

Nevertheless, one attractive feature of the results of the present study is the potential for an intervention at the public health level. Programmes that aim to reduce the prevalence of omega 3 insufficiency in pregnant women could translate into a lower incidence of cognitive impairments and possibly certain mental problems, such as schizophrenia, in their offspring. Just as folate supplementation has been shown to reduce the incidence of neural tube defects (Czeizel & Dudás, 1992), attention to certain nutrients (vitamin D status) could reduce the incidence of schizophrenia.

Future studies should conduct a rigorous evaluation of the association between dietary behaviour across critical periods of development and cognitive functions and psychosis by looking at the nutrition intake prenatally through childhood and then adulthood. Up to date there is no a single cohort available to assess this. My thesis examined nutritional intake in pregnancy and child cognitive performance. It would be valuable to provide longitudinal data to examine the relation between children' consumption of food rich in omega 3 in the years after birth and cognitive functioning and school performance, and mental health symptoms.. Thirdly, to examine further impact of nutrients on cognition and possible psychotic and depressive symptoms, it should be considered to look at the link between multiple nutrients and psychotic like symptoms in adulthood. The objective should be to look not only at omega 3 intakes but also to investigate multiple nutrients and the longitudinal relation between their consumption and psychotic and depressive symptoms in adults. In short, an ideal research project should provide a robust evidence for the ongoing debate on the role of nutrition through the lifespan as a possible risk factor for cognitive impairment and mental illness such as depression and psychosis. We attempted to examine this, however, considering lack of resources and PhD timelines, we lacked a complete evaluation of nutrients intake across lifespan as we only could access the data for prenatal nutrients (meta-analysis) and middle aged females (Swedish cohort). Also, to further strengthen an association between nutrients and mental health it would be valuable to assess

confounding by parental psychiatric history as well as information on psychiatric admissions from patients' registry.

Focusing on vitamin D, my results should motivate further longitudinal and experimental studies demonstrating consistent time-sequenced associations in order to further explore causality in the mental health-vitamin D link. Validating an involvement of vitamin D from sun exposure in the pathway to mental health problems such as psychosis and depression may have important implications. Although low levels of vitamin D are highly prevalent, potentially modifiable determinants of vitamin D status, such as dietary habits, use of dietary supplements and more importantly, behaviour related to sun exposure, could provide new selective cost-effective strategies aimed at preventing psychosis and/or depression, and their disease burden. Although there is much more work to be done, if future studies confirm the association between vitamin D deficiency and risk of mental health (schizophrenia or depression), it could increase the prospect of the primary prevention of mentioned mental problems in a comparable way to folate supplementation for the prevention of spina bifida (Czeizel & Dudás, 1992; Czeizel, Dudás, Vereczkey, & Bánhid, 2013).

Appendices

Appendix A.

Women's Lifestyle and Health questionnaires

1. In which country were you mainly resident for the first 7 years of life?

- ☐ 1 Sweden
- ☐ 2 Finland
- ☐ 3 Norway
- ☐ 4 Denmark
- ☐ 5 Other

2. Total number of years of education (include compulsory school)

..... years

PERSONAL DESCRIPTION

69. Which is your natural hair color?

- ☐ 1. Dark brown/black
- ☐ 2. Light brown
- ☐ 3. Blonde
- ☐ 4. Red

70. Which is your eye color?

- ☐ 1. Brown
- ☐ 2. Grey/Green
- ☐ 3. Blue

71. Do you have freckles on your arms?

- ☐ 1. No
- ☐ 2. Yes, a few
- ☐ 3. Yes, many

72. How does your skin react to the sun at the beginning of the summer?

- ☐ 1. It becomes brown without turning red
- ☐ 2. It becomes red
- ☐ 3. It becomes red and sunburned
- ☐ 4. It becomes sunburned with blisters

73. How does your skin react after lengthy sun exposure?

- ☐ 1. It becomes dark brown
- ☐ 2. It becomes brown
- ☐ 3. It becomes light brown
- ☐ 4. It never gets brown

74. How often are you using sun lotion when sun bathing?

- ☐ 1. Never
- ☐ 2. Irregularly
- ☐ 3. Every two days
- ☐ 4. Almost always

75. How many dysplastic naevi – larger than 5 mm – do you have totally on your legs (from toes to groins)?

- ☐ 1. None.
- ☐ 2. One naevi
- ☐ 3. 2-3 naevi
- ☐ 4. 4-6 naevi
- ☐ 5. 7-12 naevi
- ☐ 6. 13-24 naevi
- ☐ 7. 25 or more

76. At different ages, how many times did you get sunburned with blisters and peeling skin?

- ☐ 1. Never
- ☐ 2. Once
- ☐ 3. 2-3 times
- ☐ 4. 4-5 times
- ☐ 5. 6 times or more

77. At different ages, how many weeks per year do you take a vacation at the beach (in Sweden or abroad)?

- ☐ 1. Never
- ☐ 2. 1 week
- ☐ 3. 2-3 weeks
- ☐ 4. 4-6 weeks
- ☐ 5. 7 weeks or more

78. At different ages, how many times did you go to the solarium per month?

- ☐ 1. Never
- ☐ 2. Rarely
- ☐ 3. Once
- ☐ 4. Twice
- ☐ 5. 3-4 times
- ☐ 6. 5 times or more

FOOD FREQUENCY DURING THE LAST YEAR

79. What type and how much milk do you drink per day or per week, including milk used in porridge, stewed fruit, coffee? (1 glass = 2 dl)

Light milk (0.5% fat or less)	glasses/day	glasses/week
Medium milk (1.5% fat)	glasses/day	glasses/week
Standard milk (3% fat)	glasses/day	glasses/week
Sour milk/yoghurt/kefir	glasses/day	glasses/week
Sour milk light/yoghurt light	glasses/day	glasses/day

- ☐ 1. I hardly ever drink or use milk

80. What type and how much bread do you eat per day or week?

White bread	slices/day	slices/week
Whole grain bread	slices/day	slices/week
Sweet bread/rusks	slices/day	slices/week
Crisp bread	slices/day	slices/week

81. How many open sandwiches spread with butter/margarine do you eat per day or week?

... slices/day slices/week

82. What kind of fat are you using for sandwiches and cooking (baking included)?

	Sandwiches	Cooking/baking
Butter		
Bregott (butter/margarine mixture)		
Table margarine (Flora, Vår)		
Low-fat margarine (Lätt & Lagom, Lätta)		
Margarine (hard from fridge)		
Cooking oil (maize, sunflower, soy)		
Canola oil		
Olive oil		

☐ 1. I don't use fat in cooking

☐ 2. I don't use fat on my sandwiches → Proceed to question number 84

83. How thick do you butter your bread?

☐ 1. Fairly thick

☐ 2. Thin

☐ 3. Very thin

84. How often do you eat the following kinds of cheese, and how much – number of slices or tablespoons/day, number of slices or tablespoons/week?

	Slices/tablespoons/day	Slices/tablespoons/week
Regular cheese		
Low fat cheese		
Spread cheese		
Low fat spread cheese		
Cottage cheese		

☐ 1. I eat cheese infrequently or not at all

85. How many cups of coffee do you drink per day or per week? (1 cup is 1,5 dl).

86. cups/day cups/week

☐ 1. I drink coffee seldom or not at all

87. How much alcohol do you drink per week, month or year?

Glass/week Glass/month Glass/year

Class II beer (1 glass = 2 dl)
 Class III beer (1 glass = 2 dl)
 Wine (1 glass = 1 dl)
 Fortified wine (1 glass = 4 cl)
 Distilled spirits (1 glass = 4 cl)

☐ 1. I drink alcoholic beverages seldom or not at all

88. What do you do with the visible fat on meat and the skin on chicken and other poultry?

☐ 1. Eat all

☐ 2. Eat some

☐ 3. Cut off as much as possible

89. How often and how much of the following food items have you eaten during the last year?

Check appropriate box for how often and how much. (If you never or seldom eat a specific food item, you don't need to check the how much box).

SMALL portion = half of a MEDIUM portion or less.

LARGE portion = one and a half of a MEDIUM portion or more.

The size of a median portion is indicated for each food item in parentheses.

Food item	How often									How much			
	Seldom Never	Per Month	Per week					Per day			Your portion during the last year		
			1-3	1	2	3-4	5-6	1	2	3			
											Small	Medium	Large
Oatmeal porridge (250 ml)													
Other porridge, gruel (250 ml)													
Dry cereal/müsli (200 ml)													
Spaghetti/macaroni (200 ml)													
Rice (200 ml)													
Wheat or oat bran (1 tablespoon)													
Boiled potatoes (2 potatoes or 200 ml)													
Fried potatoes (200 ml)													

Meat and sausage
Fish
Fat/oil in cooking

93. Are you using vitamins, minerals or any other nutritional supplements?

☐ 1. No, never → Proceed to question number 94

☐ 2. Yes, regularly or now and then

93. What kind of vitamins, minerals and nutritional supplements and how much are you using?

	Name	No. of tablets/ week	No. of weeks/ year
	Multivitamin		
	Vitamin C		
	Vitamin A		
	Vitamin E		
	B-vitamins		
	Kalcium		
	Magnesium		
	Selen		
	Zinc		
	Iron		
	Caroten		
	Fish oil		
	Other, state:		

Appendix B.

Women's Lifestyle and Health follow up questionnaire

Attitudes and feelings

16. Have you ever felt sad, down or depressed two weeks or longer in a row?

☐ Yes (continue to question 16a)

☐ No (continue to question 17)

a) How long did this feeling of sadness, being down or depressed usually last during that period?

☐ All day ☐ Most of the day ☐ About half the day ☐ Less than half the day

b) During that period, did you feel like that:

☐ Every day

☐ Almost every day

☐ Less often

c) How old were you the first time you experienced a period of at least two weeks in a row when you felt sad, down or depressed? State your age: _____

17. Has there ever been a time period which has lasted two weeks or more, when you've lost all interest in most things in life, such as work, hobbies or some other occupation you usually enjoy?

☐ Yes (continue to question 17a) ☐ No (continue to question 18)

a) How long did this feeling of lost interest last during this period?

☐ All day ☐ Most of the day ☐ About half the day ☐ Less than half the day

b) During that period, did you feel like that:

☐ Every day

☐ Almost every day

☐ Less often

c) Did you feel tired constantly and without any energy?

☐ Yes

☐ No

d) During this period, did your weight change even though you didn't try to make it change?

☐ Kept my weight

☐ Lost weight *Approximately how much did you lose? (State in kilograms)* F17_9_11

☐ Gained weight *Approximately how much did you gain? (State in kilograms)* F17_7_12

☐ Both gained and lost weight *Approximately how much did you gain or lose (state in kilograms)* _____

3 e) During this period, did you find it more difficult to fall asleep than usual?

☐ Yes ☐ No (continue to question g)

4 f) How often did you find it difficult to fall asleep during this period?

☐ Every night ☐ Almost every night ☐ Less often

5 g) Did you find it more difficult than usual to concentrate?

☐ Yes

☐ No

6 h) Sometimes people look down on themselves feel bad or useless. Did you feel that way?

☐ Yes

☐ No

7 i) Did you think a lot about death, either your own or somebody else's or death in general?

☐ Yes

☐ No

8 j) How old were you the first time you experienced a period of at least two weeks, when you've lost all interest in most things in life (and had problems with tiredness, keeping your weight, sleeping, concentration, self-confidence, thoughts about death)?

State your age: _____

9 k) How many times have you felt this way during your lifetime?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 times or more

0 l) How old were you the last period when you felt like this? State your age: _____

18. Have you ever experienced a time period which has lasted a month or longer when you felt worried and anxious most of the time?

☐ Yes (continue to question 19)

☐ No (continue to question 22)

19. Are you still experiencing this or has the period stopped?

☐ Still feel that way

☐ It has stopped

a) How long did/does it last, counted in months or years?

☐ Months: F19_3

☐ Years: F19_6

☐ All my life

b) Do you or did you worry about things that probably won't or can't happen?

☐ Yes

☐ No

c) Do you or did you worry about things that aren't or weren't especially important?

☐ Yes

☐ No

20. Have you then been preoccupied by different kinds of trouble at the same time?

21. When you are or were worried and anxious: (Mark as many options as you like)

☐ Are/were you also restless?

☐ Are/were you also wound up and on edge?

☐ Are/were you also very easily irritated?

☐ Do you/did you also get palpitations of the heart?

☐ Do/did you easily get tired?

☐ Do/did you also have problems falling asleep or wake up again once you'd fallen asleep

☐ Do/did you feel lethargic, ready to faint or unreal?

☐ Do/did your muscles feel tense, sore or aching?

22. The following questions aim to measure different feelings and experiences that most people have during their life time. Answer as honestly as possible. There are no right or wrong answers.

	Never	Sometimes	Often	Nearly always
Do you ever feel as if other people make remarks aimed at you and that they say thing that may be ambiguous?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever feel that what is written in the papers or is said on TV may be aimed especially at you?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever feel that other people aren't who they say they are?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever feel that you are stalked in some way?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever feel that there is a conspiracy against you?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever feel that you are meant to be somebody really important?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever feel that you are a very special or rare person?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever think that people can communicate by telepathy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever feel that electric devices can influence your thinking?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you believe in witchcraft, voodoo or occult phenomena?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever feel that people are looking strangely at you because of your appearance?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever feel that that your thoughts are taken from your head?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever feel that the thoughts in your head aren't your own?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have your thoughts ever been so intense that you've been worried that other people may hear them?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever hear your own thoughts bounce back at you like an echo?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever feel that you are controlled by some power or thing outside of yourself?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever hear voices when you're alone?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever hear voices speaking to each other when you're alone?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever feel like a double has taken the place of a family member, friend or acquaintance?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you ever see objects, people or animals that others can't see?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Appendix C.

SAS program for the quantile regression analysis

```
*-- SAS formats -----;
proc format;

    value educat 1='0-10yrs' 2='11-13yrs' 3='>13yrs';
    value bmifmt 1='<25' 2='25-29.9' 3='>30';
    value cunlfmt 0='Never' 1='1 week' 2='2 weeks';
    value solbfmt 0='None' 1='1 time' 2='2 time';
    VALUE NEWHOLS 0='Never' 1='2 weeks' 2='1 week';
    VALUE NEWBURN 0='None' 1='2 times' 2='1 time';
RUN;

run;

*-- Main program -----
-----;
*Create plot of side by side bars for CAPE items;
*-----;
data pl;
    label cape='CAPE mean score';
    set study.wlh_cohort2;
    keep lpnr cape f22_1 f22_2 f22_3 f22_4 f22_5 f22_6 f22_7
        f22_8 f22_9 f22_10 f22_11 f22_12 f22_13
        f22_14 f22_15 f22_16 f22_17 f22_18 f22_19
f22_20;

    *- Code 9 is a missing code;
    if f22_1 > 7 then f22_1 = .m;
    if f22_2 > 7 then f22_2 = .m;
    if f22_3 > 7 then f22_3 = .m;
    if f22_4 > 7 then f22_4 = .m;
    if f22_5 > 7 then f22_5 = .m;
    if f22_6 > 7 then f22_6 = .m;
    if f22_7 > 7 then f22_7 = .m;
    if f22_8 > 7 then f22_8 = .m;
    if f22_9 > 7 then f22_9 = .m;
    if f22_10 > 7 then f22_10 = .m;
    if f22_11 > 7 then f22_11 = .m;
    if f22_12 > 7 then f22_12 = .m;
    if f22_13 > 7 then f22_13 = .m;
    if f22_14 > 7 then f22_14 = .m;
    if f22_15 > 7 then f22_15 = .m;
    if f22_16 > 7 then f22_16 = .m;
    if f22_17 > 7 then f22_17 = .m;
    if f22_18 > 7 then f22_18 = .m;
    if f22_19 > 7 then f22_19 = .m;
    if f22_20 > 7 then f22_20 = .m;

    cape= mean(f22_1,f22_2,
f22_3,f22_4,f22_5,f22_6,f22_7,f22_8,f22_9,f22_10,f22_11,f22_12,f22_13,
f22_14,f22_15,f22_16,f22_17,f22_18,f22_19,f22_20);
    data cape_n;
        SET study.wlh_cohort2;
        n = N(f22_1,f22_2,
f22_3,f22_4,f22_5,f22_6,f22_7,f22_8,f22_9,f22_10,f22_11,f22_12,f22_13,
f22_14,f22_15,f22_16,f22_17,f22_18,f22_19,f22_20);
```

```

run;

*-- Transpose the items so each variable is one row instead;
proc sort data=p1;by lpnr;run;
proc transpose data=p1 out=p2;
  var f22_1 f22_2 f22_3 f22_4 f22_5 f22_6 f22_7
      f22_8 f22_9 f22_10 f22_11 f22_12 f22_13
      f22_14 f22_15 f22_16 f22_17 f22_18 f22_19 f22_20;
  label f22_1='Double meaning' f22_2='Messages from TV' f22_3='False
appearance' f22_4='Being persecuted'
      f22_5='Conspiracy' f22_6='Being important' f22_7='Being
special' f22_8='Telepathy' f22_9='Influenced by devices'
f22_10='Witchcraft, voodoo or the occult'
      f22_11='Odd appearance' f22_12='Thought withdrawal'
f22_13='Thought insertion' f22_14='Thought broadcasting'
f22_15='Echoed thought'
      f22_16='External control' f22_17='Verbal hallucinations'
f22_18='Voices conversing' f22_19='Capgras syndrome' f22_20='Visual
hallucinations';
  BY lpnr;

run;

*-- The item number is embedded in the variable names (now found in
the _name_ variable);
data p3;
  attrib item length=4 label='The CAPE positive scale (items 1-20)';
  keep lpnr item coll _label_;
  set p2;
  item=input(tranwrd(_name_, 'F22_', ''), 8.);
run;

*-- Compile the macro producing the figure;
%inc saspgm(ssordplt);

filename hepp 'C:\WLH\sasproj\WLH\WLH1405\sasout\ordplt1.png';

goptions device=png xpixels=1240 ypixels=800 lfactor=1
fontres=presentation
noborder cback=white htext=2 ftext="Thorndale AMT" htext=2
hby=0
display gsfname=hepp gsfmode=replace rotate=L;

%ssordplt(data=p3, class=item, classlst=1 to 20 by 1, var=coll,
ordinals=0 to 4 by 1,
          ylabel=, bystmt=, width=0.15, sidepct=%str(3,3), force=0,
zerolev=N, pattern=Y,
          missing=Y, cut=4.5 9.5,
          hsymbol=3, hangle=0, name=IVF, haxis=major=none);
filename hepp clear;
goptions reset=all;

*-- Now print the unique labels describing each item. Use this as
footnote;
proc sql;
  select distinct item, _label_ from p3
  order by item;
run;quit;

```

```

*-- Create a dataset for the sunbathing holiday variable;
data v2;
  label cum_holiday='Cumulative sun exposure from sunbathing holidays
at age 10-19 and 20-29';
  keep lpnr nsagest syden2 syden3 syden4 cum_holiday;
  set study.nosve6;
  format cum_holiday cunlfmt.;
  if syden2 <= .z and syden3 <= .z then cum_holiday=.u;
  else if syden2=0 and syden3=0 then cum_holiday=0;
  else if (syden2 <=.z and syden3=0) or (syden2=0 and syden3 <=.z)
then cum_holiday=0;
  else if (syden2 <= .z and syden3=1) or (syden2=1 and syden3 <= .z)
then cum_holiday=1;
  else if syden2=1 and syden3=1 then cum_holiday=1;
  else if (syden2=0 and syden3=1) or (syden2=1 and syden3=0) then
cum_holiday=1;
  else cum_holiday=2;
run;

data hols;
  label hols='Cumulative sun exposure from sunbathing holidays at all
3 decades (age 10-19; 20-29 and 30-39)';
  keep lpnr nsagest syden2 syden3 syden4 hols ;
  set work.v2;
  format hols cunlfmt.;
  if cum_holiday <= .z and syden4 <= .z then hols=.u;
  else if cum_holiday=0 and syden4=0 then hols=0;
  else if (cum_holiday <=.z and syden4=0) or (cum_holiday=0 and syden4
<=.z) then hols=0;
  else if (cum_holiday <= .z and syden4=1) or (cum_holiday=1 and
syden4 <= .z) then hols=1;
  else if cum_holiday=1 and syden4=1 then hols=1;
  else if (cum_holiday=0 and syden4=1) or (cum_holiday=1 and syden4=0)
then hols=1;
  else hols=2;
run;

data hols10_19;
  label hols10_19='Cumulative sun exposure from sunbathing holidays at
age 10 to 19';
  keep lpnr nsagest syden2 hols10_19;
  set study.nosve6;
  format hols10_19 NEWHOLS.;
  if syden2 <= .z then hols10_19=.u;
  else if syden2=0 then hols10_19=0;
  else if syden2=1 then hols10_19=2;
  else if syden2=> 2 then hols10_19=1;
  else hols10_19= 1;

run;

data hols20_39;
  label hols20_39='Cumulative sun exposure from history of sunburns
at age 20 to 39';
  keep lpnr nsagest hols20_39;
  set study.nosve6;
  format hols20_39 NEWHOLS.;
  if syden3 <= .z and syden4 <= .z then hols20_39=.u;
  else if syden3=0 and syden4=0 then hols20_39=2;
  else if (syden3 <=.z and syden4 =0) or (syden3=0 and syden4 <= .z)
then hols20_39 =0;
  else if (syden3 <= .z and syden4 =1) or (syden3=1 and syden4 <= .z)
then hols20_39=2;
  else if syden3=1 and syden4=1 then hols20_39=2;

```

```

    else if (syden3=0 and syden4=1) or (syden3=1 and syden4=0) then
      hols20_39=2;
    else hols20_39=1;
  run;

  *-- Create a dataset for the sunburns variable;
  data v3;
    label cum_sunburn='Cumulative number of annual sunburns at age 10 to
29';
    keep lpnr nsagest solb2 solb3 solb4 cum_sunburn;
    set study.nosve6;
    format cum_sunburn solbfmt.;
    if solb2 <= .z and solb3 <= .z then cum_sunburn=.u;
    else if solb2=0 and solb3=0 then cum_sunburn=0;
    else if (solb2 <= .z and solb3=0) or (solb2=0 and solb3 <= .z) then
      cum_sunburn=0;
    else if (solb2 <= .z and solb3=1) or (solb2=1 and solb3 <= .z) then
      cum_sunburn=1;
    else if solb2=1 and solb3=1 then cum_sunburn=1;
    else if (solb2=0 and solb3=1) or (solb2=1 and solb3=0) then
      cum_sunburn=1;
    else cum_sunburn=2;
  run;
  data sburn;
    label sburn='Cumulative number of annual sunburns at age 10-19; 20-
29 and 30-39';
    keep lpnr nsagest solb2 solb3 solb4 cum_sunburn sburn;
    set work.v3;
    format sburn solbfmt.;
    if cum_sunburn <= .z and solb4 <= .z then sburn=.u;
    else if cum_sunburn=0 and solb4=0 then sburn=0;
    else if (cum_sunburn <= .z and solb4=0) or (cum_sunburn=0 and solb4
<= .z) then sburn=0;
    else if (cum_sunburn <= .z and solb4=1) or (cum_sunburn=1 and solb4
<= .z) then sburn=1;
    else if cum_sunburn=1 and solb4=1 then sburn=1;
    else if (cum_sunburn=0 and solb4=1) or (cum_sunburn=1 and solb4=0)
then sburn=1;
    else sburn=2;
  run;

  data sburn10_19;
    label sburn10_19='Cumulative sun exposure from number of sunburns
at age 10 to 19';
    keep lpnr nsagest sburn10_19;
    set study.nosve6;
    format sburn10_19 NEWBURN.;
    if solb2 <= .z then sburn10_19=.u;
    else if solb2=0 then sburn10_19=0;
    else if solb2=1 then sburn10_19=2;
    else if solb2=> 2 then sburn10_19=1;
    else sburn10_19= 1;

  run;
  data sburn20_39;
    label sburn20_39='Cumulative sun exposure from number of sunburns
at age 20 to 39';
    keep lpnr nsagest sburn20_39;
    set study.nosve6;
    format sburn20_39 NEWBURN.;
    if solb3 <= .z and solb4 <= .z then sburn20_39=.u;
    else if solb3=0 and solb4=0 then sburn20_39=0;

```

```

    else if (solb3 <=.z and solb4=0) or (solb3=0 and solb4 <=.z) then
sburn20_39 =0;
    else if (solb3 <= .z and solb4=1) or (solb3=1 and solb4 <= .z) then
sburn20_39=2;
    else if solb3=1 and solb4=1 then sburn20_39=2;
    else if (solb3=0 and solb4=1) or (solb3=1 and solb4=0) then
sburn20_39=2;
    else sburn20_39=1;
run;

```

```

DATA NEWREF;
ATTRIB HOLS LENGTH=4 FORMAT=NEWHOLS.
LABEL= 'WEEKS ON SUNBATHING HOLIDAYS';
SET HOLS;
IF HOLS=0 THEN HOLS=0;
ELSE IF HOLS=1 THEN HOLS=2;
ELSE IF HOLS=2 THEN HOLS=1;

```

```

RUN;

```

```

DATA NEWREF2;
ATTRIB SBURN LENGTH=4 FORMAT=NEWBURN.
LABEL= 'HISTORY OF SUNBURNS';
SET SBURN;
IF SBURN=0 THEN SBURN=0;
ELSE IF SBURN=1 THEN SBURN=2;
ELSE IF SBURN=2 THEN SBURN=1;
RUN;

```

```

*-- Create the combined sun exposure dataset;

```

```

proc sort data=newref; by lpnr;run;
proc sort data=newref2; by lpnr; run;
proc sort data=hols10_19; by lpnr; run;
proc sort data=sburn10_19; by lpnr; run;
proc sort data=sburn20_39; by lpnr; run;
proc sort data=hols20_39;by lpnr;run;

```

```

data sunexp;
merge newref newref2 hols20_39 hols10_19 sburn10_19 sburn20_39 ;by
lpnr;
run;

```

```

*-- Create dataset for baseline subject characteristics;

```

```

*--- Creating bmi categories: variable bmi from dataset nosve6---* ;

```

```

data bmi;
keep lpnr nsagest BMI cbmi;
label cbmi='BMI categories' nsagest='Age at baseline';
format cbmi bmfmt.;
set study.nosve6;
if bmi <= .z then cbmi=.;
else if 0<=bmi< 25 then cbmi=1;
else if 25<=bmi<= 30 then cbmi=2;
else if 30<bmi then cbmi=3;
run;

```

```

*--- Creating categories for years in school: variable skole from
dataset nosve6---* ;
data skole;
    label    skole='Years in education'    cskole='education categories';
    keep lpnr skole cskole;
    format cskole educcat.;

    set study.nosve6;

    if skole<=.z then cskole= .;
    else if skole=<10 then cskole= 1;
    else if skole=<11 then cskole=2;
    else if skole=<13 then cskole=3;
    else cskole=3;
run;

*-----;
* Creating a baseline dataset for analysis (without CAPE scores) to
calculate missing values for baseline only;
*-----;

proc sort data=sunexp;by lpnr;run;
proc sort data=bmi; by lpnr; run;
proc sort data=skole;by lpnr; run;
data bsln(label='Baseline dataset');
    merge sunexp bmi skole;
    by lpnr;
run;

PROC SORT DATA=bsln; BY LPNR;RUN;
PROC SORT DATA=p1; BY LPNR; RUN;
proc sort data=cape_n; by lpnr;run;
DATA analys1 (LABEL='ANALYSIS DATASET BASELINE+FU');
    MERGE bsln p1 cape_n;
    BY LPNR;
RUN;

title1;footnote;
proc datasets lib=work mt=data nolist;
    delete p1 cape_n v1 v2 v3 sunexp skole
            hols sburn newref newref2 hols20_39 hols10_19 sburn10_19
sburn20_39;
quit;

*---Creating data set for follow up cohort in order to compare
demographic characteristics of the original cohort at baseline and
follow up---*;

data fu;
    set analys1;
    if n= . then delete;
run;
*---excluding women with no answers to CAPE scale---*;
data ful;
    set fu;
    if n=0 then delete;
run;

```



```

*--- CAPE means for each CAPE variable (creating table with means for
supplementary material)---*;

DATA analysismmeans;
  SET analys1 ;
  label f22_1='Double meaning' f22_2='Messages from TV' f22_3='False
appearance' f22_4='Being persecuted'
        f22_5='Conspiracy' f22_6='Being important' f22_7='Being
special' f22_8='Telepathy' f22_9='Influenced by devices'
f22_10='Witchcraft, voodoo or the occult'
        f22_11='Odd appearance' f22_12='Thought withdrawal'
f22_13='Thought insertion' f22_14='Thought broadcasting'
f22_15='Echoed thought'
        f22_16='External control' f22_17='Verbal hallucinations'
f22_18='Voices conversing' f22_19='Capgras syndrome' f22_20='Visual
hallucinations';
  keep F22_1-F22_20;
RUN;

PROC CONTENTS DATA=analysismmeans;
RUN;
PROC MEANS DATA=analysismmeans maxdec=1;
RUN;

title 'Demographic characteristics of the original cohort at baseline
and follow up';
proc means data=bsln n nmiss mean std maxdec=2;
  var skole nsagest;
run;
proc means data=ful n nmiss mean std maxdec=2;
  var skole nsagest;
run;

*--- Descriptive statistics: proc means ---*;

title 'Descriptive statistics: proc means';
Proc means data=analys1 n nmiss mean std;
  var skole nsagest;
run;
proc means data=analys1 n nmiss mean std min max maxdec=2;
var cape;
run;

title1 'Mean and summary statistics by sun exposure levels (for Table
1)';
proc means data=ful n nmiss mean std min max maxdec=1 nway;
  var skole NSAGEST;
  class hols;
  run;
proc means data=ful n nmiss mean std min max maxdec=1 nway;
  var skole NSAGEST;
  class sburn;
  run;
proc means data=ful n nmiss mean min max maxdec=1;
var skole;
run;

proc freq data=ful;
tables sburn;
run;
proc freq data=ful;

```

```

tables hols;
run;
proc means data=ful n nmiss mean min max maxdec=1;
var cape;
run;

*-----;
* Create plot of side by side bars for CAPE items ;
*-----;
title 'M1: CAPE*sburn age education';
ods graphics on;
ods output parameterestimates=pesburn;
proc quantreg data=analys1 ORDER=INTERNAL outest=est1 ci=resampling
algorithm=interior(tolerance=1.e-4);
class sburn;
model cape = sburn nsagest skole / quantile= 0.10 to 0.90 by 0.10
plot=quantplot(sburn) seed=12345;
run;

title 'M2: CAPE*hols age education';
ods output parameterestimates=peshols;
proc quantreg data=analys1 ORDER=INTERNAL outest=est1 ci=resampling
algorithm=interior(tolerance=1.e-4);
class hols;
model cape = hols nsagest skole / quantile= 0.10 to 0.90 by 0.10
plot=quantplot(hols) seed=12345;
run;

*-- Select only main exposures to plot and sort the data;
proc sort data=pesburn out=pesburn1;
where parameter='SBURN' and df>0;
by parameter levell quantile;
run;
proc sort data=peshols out=peshols1;
where parameter='HOLS' and df>0;
by parameter levell quantile;
run;

*-- Combine all results so they can be plotted together;
data pesburn2;
attrib estimate label='PEs Change vs 1 time' line length=$20
sglegend length=$30 levell label='Number of times'
quantile label='Quantile'
;

set pesburn1(in=sburn) peshols1(in=hols);

if hols then sglegend='Sunbathing holidays';
else if sburn then sglegend='History of Sunburns';
else abort;

if levell='1 time' then line='SOLID ';
else if levell='1 week' then line='SOLID ';
else line='DASHED';
run;

ods listing gpath= 'C:\WLH\sasproj\WLH\WLH1405\saspgm' image_dpi=300
;

```

```

ods graphics / reset=index imagename="sun_quantplot_1"
               width=14cm height=14cm antialias
               noborder;

title;footnote;
proc sgpanel data=pesburn2;
  panelby sglegend / columns=1 rows=2 novarname;

  band x=quantile lower=lowercl upper=uppercl / transparency=0.7
  group=levell;
  series x=quantile y=estimate / group=levell group=line
  lineattrs=(color='black' thickness=1);

  refline 0 / axis=y;
  colaxis values=(0.2 to 0.9 by 0.1);
  rowaxis min=-0.02 max=0.04 label='Change in CAPE scale ("1
time/week" as comparison group)';
run;

```

Appendix D.

SAS program/Sensitivity Analysis for the sun exposure and psychotic symptoms study

```

*---SUBGROUP ANALYSES---*;
*---Cumulative sun exposure and CAPE scores over childhood and early
adulthood age 10-19 years---*;
*-----;

title 'Exposure at childhood sunbathing holidays at age 10-19,
hols10_19';
ods graphics on;
ods output parameterestimates=peshols;
proc quantreg data=analys1 ORDER=INTERNAL outest=est1 ci=resampling
algorithm=interior(tolerance=1.e-4);
  class hols10_19;
  model cape = hols10_19 nsagest skole / quantile= 0.10 to 0.90 by
0.10 plot=quantplot(hols10_19) seed=12345;
run;

title 'Exposure at age 10-19, sburn10_19';
ods output parameterestimates=pesburn;
proc quantreg data=analys1 ORDER=INTERNAL outest=est1 ci=resampling
algorithm=interior(tolerance=1.e-4);
  class sburn10_19;
  model cape = sburn10_19 nsagest skole / quantile= 0.10 to 0.90 by
0.10 plot=quantplot(sburn10_19) seed=12345;
run;

*-- Select only main exposures to plot and sort the data;
proc sort data=pesburn out=pesburn1;
  where parameter='sburn10_19' and df>0;
  by parameter levell quantile;
run;

```

```

proc sort data=peshols out=peshols1;
  where parameter='hols10_19' and df>0;
  by parameter levell quantile;
run;

*-- Combine all results so they can be plotted together;
data pesburn2;
  attrib estimate label='PEs Change vs 1 time age 10-19' line
length=$20
          sglegend length=$30 levell label='Number of times'
          quantile label='Quantile'
  ;

  set pesburn1(in=sburn10_19) peshols1(in=hols10_19);

  if hols10_19 then sglegend='Sunbathing holidays';
  else if sburn10_19 then sglegend='History of Sunburns';
  else abort;

  if levell='1 time' then line='SOLID ';
  else if levell='1 week' then line='SOLID ';
  else line='DASHED';
run;

ods listing gpath= 'C:\WLH\sasproj\WLH\WLH1405\saspgm' image_dpi=300
;

ods graphics / reset=index imagename="sun10_19_quantplot_1"
              width=14cm height=14cm antialias
              noborder;

title;footnote;
proc sgpanel data=pesburn2;
  panelby sglegend / columns=1 rows=2 novarname;

  band x=quantile lower=lowercl upper=uppercl / transparency=0.7
group=levell;
  series x=quantile y=estimate / group=levell group=line
lineattrs=(color='black' thickness=1);

  refline 0 / axis=y;
  colaxis values=(0.2 to 0.9 by 0.1);
  rowaxis min=-0.02 max=0.04 label='Change in CAPE scale age 10-19 ("1
time/week" as comparison group)';
run;

*---Cumulative sun exp and cape scores over adulthood (20_39 years)---
*;
title 'Exposure at age hols20_39';
ods graphics on;
ods output parameterestimates=pesholsadult;
proc quantreg data=analys1 ORDER=INTERNAL outest=est1 ci=resampling
algorithm=interior(tolerance=1.e-4);
  class hols20_39;
  model cape = hols20_39 nsagest skole / quantile= 0.10 to 0.90 by
0.10 plot=quantplot(hols20_39) seed=12345;
run;

title 'Exposure at age sburn20_39';
ods output parameterestimates=pesburnadult;

```

```

proc quantreg data=analys1 ORDER=INTERNAL outest=est1 ci=resampling
algorithm=interior(tolerance=1.e-4);
  class sburn20_39;
  model cape = sburn20_39 nsagest skole / quantile= 0.10 to 0.90 by
0.10 plot=quantplot(sburn20_39) seed=12345;
run;

*-- Select only main exposures to plot and sort the data;
proc sort data=pesburnadult out=pesburnadult1;
  where parameter='sburn20_39' and df>0;
  by parameter levell quantile;
run;
proc sort data=pesholsadult out=pesholsadult1;
  where parameter='hols20_39' and df>0;
  by parameter levell quantile;
run;

*-- Combine all results so they can be plotted together;
data pesburnadult2;
  attrib estimate label='PEs Change vs 1 time age 20-39' line
length=$20
          sglegend length=$30 levell label='Number of times'
          quantile label='Quantile'
  ;

  set pesburnadult1(in=sburn20_39) pesholsadult1(in=hols20_39);

  if hols20_39 then sglegend='Sunbathing holidays';
  else if sburn20_39 then sglegend='History of Sunburns';
  else abort;

  if levell='1 time' then line='SOLID ';
  else if levell='1 week' then line='SOLID ';
  else line='DASHED';
run;

ods listing gpath= 'C:\WLH\sasproj\WLH\WLH1405\saspgm' image_dpi=300
;

ods graphics / reset=index imagename="sun20_39_quantplot_1"
              width=14cm height=14cm antialias
              noborder;

title;footnote;
proc sgpanel data=pesburnadult2;
  panelby sglegend / columns=1 rows=2 novarname;

  band x=quantile lower=lowercl upper=uppercl / transparency=0.7
group=levell;
  series x=quantile y=estimate / group=levell group=line
lineattrs=(color='black' thickness=1);

  refline 0 / axis=y;
  colaxis values=(0.2 to 0.9 by 0.1);
  rowaxis min=-0.02 max=0.04 label='Change in CAPE scale age 20-39 ("1
time/week" as comparison group)';
run;

```

```

*--HOST CHARACTERISTICS RELATED TO UV SENSITIVITY:X_SOLLENGE,
SOLSTART, HARFARGE, OYEFARGE,
SSKREM AND CAPE SCORES---*;

data sensitive;
keep lpnr nsagest skole solstart;
set study.nosve6;
run;

data skin;
keep lpnr x_sollenge v205 v206 v207 v208;
set study.ns;
run;

data sensitive2;
keep lpnr hols sburn nsagest skole cape;
set work.analys1;
run;

proc sort data=sensitive; by lpnr;run;
proc sort data=sensitive2; by lpnr; run;
proc sort data=skin; by lpnr; run;
data skintype;
merge sensitive skin sensitive2; by lpnr; run;

*-- Cleanup -----
-----;
title1;footnote;
proc datasets lib=work mt=data nolist;
  delete sensitive skin sensitive2 ;
run;
quit;

*****;

title 'HOST CHARACTERISTICS RELATED TO UV SENSITIVITY:solstart';
ods pdf;
ods graphics on;
proc quantreg ci=resampling ORDER=INTERNAL
algorithm=interior(tolerance=1.e-4)
  data=skintype ;

  class hols;
  model cape = hols nsagest skole solstart /
    quantile=0.05,0.1 to 0.9 by 0.1,0.95
    seed=1234567
    plot=quantplot;

run;

ods graphics off;

ods pdf;
ods graphics on;
proc quantreg ci=resampling ORDER=INTERNAL
algorithm=interior(tolerance=1.e-4)
  data=skintype ;

  class sburn;
  model cape = sburn nsagest skole solstart /
    quantile=0.05,0.1 to 0.9 by 0.1,0.95
    seed=1234567
    plot=quantplot;

```

```

run;

ods graphics off;

*--Predict probabilities of participating in follow up based on
baseline characteristics;
title1;footnote;
data dropouts;
  length ind 3;
  set analys1 (keep=lpnr nsagest cbmi skole hols sburn cape);
  if cape = . then ind=1; else ind=0;
run;

proc logistic data=dropouts;
  class cbmi hols sburn hols;
  model ind(event='1') = cbmi skole hols sburn hols ;
  output out=t3 XBETA=ps_xb STDXBETA= ps_sdxs PREDICTED = ps_pred;
run;

title1;footnote;
*--Create the IPW weights;
data dropouts1;
  keep lpnr ipw;
  set t3;
  IPW = 1/ps_pred;
  if ipw > .z ;
run;

*-- distribution of weights;
proc means data=dropouts1 min max p99 p1 p25 p75 maxdec=2;
var ipw;
run;

*-- Join in the weights to the analysis dataset;
proc sql;
  create table dropouts1 as
  select a.*, b.ipw
  from dropouts as a
  left join dropouts1 as b
  on a.lpnr=b.lpnr
  ;
run;quit;

*-- Apply the weights;
ods graphics on;
ods output parameterestimates=pesburn;
proc quantreg data=dropouts1 ORDER=INTERNAL outest=est1 ci=resampling
algorithm=interior(tolerance=1.e-4);
  class sburn;
  model cape = sburn nsagest skole / quantile= 0.10 to 0.90 by 0.10
plot=quantplot(sburn) seed=12345;
run;

ods output parameterestimates=peshols;
proc quantreg data=dropouts1 ORDER=INTERNAL outest=est1 ci=resampling
algorithm=interior(tolerance=1.e-4);
  class hols;

```

```

    model cape = hols nsagest skole / quantile= 0.10 to 0.90 by 0.10
plot=quantplot(sburn) seed=12345;

run;

*-- Select only main exposures to plot and sort the data;
proc sort data=pesburn out=pesburn1;
    where parameter='SBURN' and df>0;
    by parameter levell quantile;
run;
proc sort data=peshols out=peshols1;
    where parameter='HOLS' and df>0;
    by parameter levell quantile;
run;

*-- Combine all results so they can be plotted together;
data pesburn2;
    attrib estimate label='PEs Change vs 1 time' line length=$20
           sglegend length=$30 levell label='Number of times'
           quantile label='Quantile'
    ;

    set pesburn1(in=sburn) peshols1(in=hols);

    if hols then sglegend='Sunbathing holidays';
    else if sburn then sglegend='History of Sunburns';
    else abort;

    if levell='1 time' then line='SOLID ';
    else if levell='1 week' then line='SOLID ';
    else line='DASHED';
run;

ods listing gpath= 'C:\WLH\sasproj\WLH\WLH1405\saspgm' image_dpi=300
;

ods graphics / reset=index imagename="sunwights_quantplot_1"
              width=14cm height=14cm antialias
              noborder;

title;footnote;
proc sgpanel data=pesburn2;
    panelby sglegend / columns=1 rows=2 novarname;

    band x=quantile lower=lowercl upper=uppercl / transparency=0.7
group=levell;
    series x=quantile y=estimate / group=levell group=line
lineattrs=(color='black' thickness=1);

    refline 0 / axis=y;
    colaxis values=(0.2 to 0.9 by 0.1);
    rowaxis min=-0.02 max=0.04 label='Change in CAPE scale (compared to
"1 time/week")';
run;

*-- end of sensitivity analysis ---*;

```


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